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**REPRODUCIBILITY OF HEART RATE RECOVERY IN PATIENTS
WITH INTERMITTENT CLAUDICATION**

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Key Words:	peripheral arterial disease, exercise, autonomic function, reliability, agreement

REPRODUCIBILITY OF HEART RATE RECOVERY IN PATIENTS WITH INTERMITTENT CLAUDICATION

Short title: heart rate recovery reproducibility in intermittent claudication.

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5 **Background.** Post-exercise heart rate recovery (HRR) is a non-invasive tool for cardiac
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autonomic function assessment. Reproducibility of HRR has been established in healthy
subjects; however, no study has evaluated this reproducibility in clinical populations who
may present autonomic dysfunction. Patients with peripheral artery disease and intermittent
claudication (IC) often present altered cardiac autonomic function and HRR could be an
interesting tool for evaluating autonomic responses to interventions in this population.
Therefore, the reproducibility of HRR should be determined in this specific population.

Objective. To determine the reproducibility of HRR indices in patients with IC.

Methods. Nineteen men with IC underwent two repeated maximal treadmill tests. Raw HR
and relative HRR (difference to exercise peak) indices measured at 30, 60, 120, 180, 240
and 300s of recovery were evaluated. The presence of systematic bias was assessed by
comparing test and retest mean values via paired *t*-test. Reliability was assessed by
intraclass correlation coefficient (ICC), and agreement by typical error (TE), coefficient of
variation (CV) and minimal detectable difference (MDD).

Results. There were no significant differences between the test and retest values of all raw
HR and relative HRR indices ($p \geq 0.05$), except for HR120s ($p = 0.032$). All indices exhibited
excellent reliability ($ICC \geq 0.78$). Raw HR and relative HRR indices showed $TE \leq 6.4$ bpm
and $MDDs \leq 17.8$ bpm. In addition, all indices showed $CVs \leq 13.2\%$, except HRR30s
($CV = 45.6\%$).

Conclusions. The current results demonstrated that most HRR indices were highly
reproducible with no systematic error, excellent reliability and good agreement in patients
with IC following maximal graded exercise.

Keywords: peripheral arterial disease, exercise, autonomic function, reliability, agreement.

INTRODUCTION

Immediately after exercise, heart rate (HR) exponentially decays towards its pre-exercise levels with this response mediated by the autonomic nervous system (Perini et al., 1989; Imai et al., 1994; Coote, 2010; Peçanha et al., 2014). This decay represents a normal response to return the body to resting homeostatic function (Luttrell & Halliwill, 2015). The kinetics of the post-exercise heart rate recovery (HRR) reveals two phases with different physiological meanings. The first phase consists of a rapid reduction of post-exercise HR that is primarily determined by parasympathetic reactivation (Imai et al., 1994), while the second phase consists of a slow reduction that is predominantly determined by sympathetic withdrawal (Perini et al., 1989). For this reason, HRR is used as a non-invasive tool to evaluate the integrity of the cardiac autonomic nervous system.

HRR is reduced in several clinical conditions, such as cardiovascular and pulmonary diseases (Morshedi-Meibodi et al., 2002; Racine et al., 2003; Lipinski et al., 2004; Erdogan et al., 2011; Gupta et al., 2013), autoimmune diseases (Dogdu et al., 2010; Akgul et al., 2011), neurodegenerative disorders (Kanegusuku et al., 2016), among others. Despite these well-reported reduced HRR in clinical populations, there is scarce information about the reproducibility of HRR. To the best of our knowledge, studies assessing HRR reproducibility have been limited to healthy populations (Yawn et al., 2003; Bosquet et al., 2008; Al Haddad et al., 2011; Arduini et al., 2011; Tulumen et al., 2011; Dupuy et al., 2012; Boullosa et al., 2014). As lower HRR has been associated with greater overall (Cole et al., 1999; Mora et al., 2003) and cardiovascular (Mora et al., 2003) mortality rates, a greater understating of the reproducibility of HRR for clinical populations

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4 is vital. This knowledge is fundamental for research and in clinical settings, since the level
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6 of reproducibility of HRR indices will affect their capacity to predict mortality and to detect
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8 real effects of interventions (Atkinson & Nevill, 1998).
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12 Peripheral artery disease (PAD) is a clinical condition characterized by a narrowing
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14 of the arteries of the lower limbs that results in ischemia and pain in the leg during walking
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16 that releases with rest, known as intermittent claudication (IC) (Hirsch et al., 2006; Kröger
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18 et al., 2006; Makdise et al., 2008). Patients with IC often present altered cardiac autonomic
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20 function (Goernig et al., 2008; Lima et al., 2016) characterized by increased cardiac
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22 sympathetic and decreased cardiac parasympathetic modulations (Goernig et al., 2008).
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24 This impaired function might contribute to the high cardiovascular risk in this population
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26 (Imai et al., 1994). In addition, a previous study (Mahé et al., 2011) showed an inverse
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28 relationship between exercise-induced lower-limb ischemia and HRR. Therefore, HRR
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30 could be an interesting tool for these patients.
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36 Based on previous background, the current study was designed to determine the
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38 reproducibility of different indices of HRR in patients with IC.
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42 **METHODS**

43 **Participants**

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49 Patients with IC registered at a tertiary center specialized in vascular disease
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51 participated in this study. Due to the differences in the exercise responses between males
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53 and females, and the possible influence of menstrual cycle phase on the reproducibility of
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55 the physiological responses to exercise, which imposes a special study design for
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4 evaluating women, the current study only included men. All patients met the following
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6 criteria: 1) age ≥ 50 years; 2) diagnosed with Fontaine stage II of PAD; 3) ankle brachial
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8 index at rest ≤ 0.90 in at least one lower limb; 4) capacity to walk on a treadmill at 2.0 mph
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10 for at least two minutes; 5) resting systolic and diastolic blood pressures lower than
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12 160/105 mmHg, respectively; 6) absence of revascularization surgery or angioplasty in the
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14 previous year; and 7) not taking β -blockers or non-dihydropyridine calcium channel
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16 antagonists. The exclusion criteria were: 1) walking capacity limited by factors other than
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18 claudication (e.g. orthopedic limitations, neurological impairment or dyspnea); 2)
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20 electrocardiographic abnormalities suggestive of myocardial ischemia or arrhythmia during
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22 a graded maximal treadmill test; and 3) presence of diabetes with clinic cardiovascular
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24 autonomic neuropathy.
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30 The study's protocol was registered at the Brazilian Clinical Trials
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32 (<http://www.ensaiosclinicos.gov.br>, RBR-7m3d8w), was approved by the Joint Committee
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34 on Ethics of Human Research of the School of Physical Education and Sport at the
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36 University of São Paulo (process 2008/55), and written informed consent was obtained
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38 from the patients.
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45 **Procedures**

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47 Initially, the patients underwent a preliminary visit comprising of an interview and
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49 physical examination for the collection of patients' characteristics, such as age, height,
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51 mass, body mass index, presence of cardiovascular risk factors, comorbidities conditions
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53 and current medications. In addition, all patients underwent, at least, two practice graded
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55 treadmill tests before the formal collection period. This practice procedure was essential to
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4 ensure optimal performances as assessment of reproducibility has been shown to be
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6 influenced by the degree of familiarization with the exercise testing procedures (Gardner et
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8 al., 1991).
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11 After familiarization, all patients underwent two repeated maximal cardiopulmonary
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13 treadmill tests performed on different occasions with an interval of at least 3 weeks
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15 between them. Both test and retest were conducted by the same research team, at the same
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17 time of day, and in a laboratory with controlled temperature (20 to 22°C). Patients were
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19 instructed to maintain the same daily habits before all repeated tests as follow: having a
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21 light meal 2 hours before the tests, not smoking nor ingesting caffeine for at least 12 hours,
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23 and avoiding intense physical efforts in the previous 24 hours before tests.
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30 **Maximal Treadmill Exercise Test**

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32 The graded maximal treadmill exercise tests followed a protocol previously utilized
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34 for patients with IC (Gardner et al., 1991). Treadmill speed was maintained at 2.0 mph with
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36 grade commencing at 0% and increased by 2% every 2 minutes until patients were unable
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38 to walk because of leg pain (i.e. maximal claudication pain). Immediately after this exercise
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40 phase, patients lay down and remained resting in supine position during 5 minutes of
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42 recovery. HR was continuously assessed, and recorded by electrocardiography (Cardio
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44 Perfect MD, Netherlands) at rest, during exercise and in the recovery phase. Blood pressure
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46 was also assessed at rest and every two minutes during the exercise. Peak HR was
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48 determined as the highest value achieved during the exercise phase.
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56 **Heart rate recovery analysis**

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HRR was expressed by both raw and relative indices. Raw HR indices were defined as HR values measured at 30 (HR30s), 60 (HR60s), 120 (HR120s), 180 (HR180s), 240 (HR240s) and 300s (HR300s) of recovery. Relative HRR indices were defined as the absolute differences between peak HR and the HR values measured at 30 (HRR30s), 60 (HRR60s), 120 (HRR120s), 180 (HRR180s), 240 (HRR240s) and 300s (HRR300s) of recovery.

Statistical Analyses

Values are expressed as mean \pm standard deviation (SD). The normality of all data was checked by the Shapiro-Wilk test, and the presence of heteroscedasticity by the coefficient of correlation between the mean values of the test and retest and the absolute difference between them (Atkinson & Nevill, 1998). The reproducibility of raw HR and relative HRR indices was assessed by the following parameters: 1) presence of systematic bias; 2) reliability; and 3) agreement (Atkinson & Nevill, 1998; de Vet et al., 2006).

The presence of systematic bias was assessed by comparing the test and retest values via a paired *t* test, and considering $p \leq 0.05$ as significant.

Reliability was examined via intraclass coefficient correlation (ICC) with reliability considered poor if ICC was < 0.40 , fair to good if ICC was between 0.40 and 0.74, and excellent if ICC was ≥ 0.75 (Rosner, 2011).

As all variables exhibited a normal distribution and an absence of heteroscedasticity, agreement was evaluated by typical error (TE) expressed in beats per minute (bpm), with a small TE representing good agreement (Atkinson & Nevill, 1998; Hopkins, 2000; de Vet et al., 2006). In addition, to improve the comparison between the

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4 different HRR indices (Atkinson & Nevill, 1998), agreement was also expressed by
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6 coefficient of variation (CV), which was calculated by the quotient between TE and the
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8 mean value of the test and retest values (Hopkins, 2000). Minimal difference detectable
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10 (MDD), which is the minimal difference that can be attributed to a real difference between
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12 repeated tests and not to random variation, was also derived from TE, using the following
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14 formula: $1.96 \times \sqrt{2} \times TE$ (de Vet et al., 2006). Finally, Bland and Altman plots with 95%
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16 limits of agreement (LOA) were also calculated and demonstrated as previously described
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18 (Bland & Altman, 1986).
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25 26 RESULTS

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28 Eighty-four patients were invited to participate and 56 agreed and underwent the
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30 preliminary procedures. In this phase, two subjects were excluded because of the presence
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32 of diabetes with clinic cardiovascular autonomic neuropathy. Thus, 54 subjects performed
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34 the maximal cardiopulmonary treadmill test and another five were excluded (3 presented
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36 electrocardiographic abnormalities and 2 did not present intermittent claudication
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38 symptom). Thus, of the remaining 49 patients, 20 were randomly selected to perform the
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40 second maximal cardiopulmonary treadmill test. Lastly, one patient was excluded due to
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42 technical problems that precluded data analysis. Therefore, 19 patients with IC formed the
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44 sample of this study, and their clinical characteristics are shown in Table 1. There were no
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46 significant differences in the test results between the included and non-included patients
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48 (data not shown).
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54 In general, patients were elderly (age > 60 years old), with several cardiovascular
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56 risk factors and presented with an ankle brachial index between 0.41 and 0.90 (mild to
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4 moderate PAD). Patients were taking different medications, e.g. aspirins, statins, anti-
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moderate PAD). Patients were taking different medications, e.g. aspirins, statins, anti-hypertensives and maintained their medication regime throughout this study.

Test duration, total walked distance, raw HR and relative HRR indices obtained in the test and retest, as well as the differences between them are shown in Table 2. There were no significant differences (systematic bias) between test and retest mean values for all variables ($p > 0.05$), except for HR120s ($p = 0.032$).

Reliability and agreement data for HRR are shown in Table 3. The raw HR indices showed ICCs ranging from 0.820 to 0.938, while the relative HRR indices exhibited ICCs between 0.781 and 0.926. Regarding agreement, the raw HR indices exhibited TEs and MDDs ranging from 5.4 to 6.4 bpm and 14.9 to 17.8 bpm, while the relative HRR indices presented TEs and MDDs ranging from 3.0 to 4.0 bpm and 8.2 to 11.1 bpm. When agreement was expressed by CV, the raw HR indices presented CVs $\leq 7.2\%$, while relative HRR indices presented CVs ≤ 13.2 , with the exception of HRR30s (CV = 45.6 %).

The Bland & Altman's plots for the raw HR and relative HRR indices are shown in Figures 1 and 2, respectively. The visual inspection of Bland-Altman plots reinforces the absence of heteroscedasticity and systematic bias of HRR indices.

DISCUSSION

The main finding of this study was that most raw HR and relative HRR indices were highly reproducible in patients with IC.

As there were no significant differences between test and retest mean values for all indices of HRR, except HR120s, it is possible to state that, in general, there is no systematic error between test and retest. Similarly, previous studies with healthy subjects

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4 also reported absence of systematic bias in raw HR (Bosquet et al., 2008; Tulumen et al.,
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6 2011; Boullosa et al., 2014) and relative HRR (Bosquet et al., 2008; Al Haddad et al., 2011;
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8 Arduini et al., 2011; Tulumen et al., 2011; Dupuy et al., 2012; Boullosa et al., 2014)
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10 indices.
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14 The current study observed an excellent reliability ($ICC \geq 0.78$) for all raw HR and
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16 relative HRR indices, suggesting that all indices can be used for distinguishing patients
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18 with IC from each other (Atkinson & Nevill, 1998; de Vet et al., 2006). Similarly, the study
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20 of Dupuy et al. (2012) also demonstrated an excellent reliability ($ICC \geq 0.80$) for both raw
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22 HR and relative HRR indices in healthy subjects. Moreover, Boullosa et al. (2014) also
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24 showed excellent reliability for all these indices ($ICC \geq 0.78$), except for HRR60s.
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28 Regarding agreement, both raw HR and relative HRR indices showed good
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30 agreement represented by low TEs ≤ 6.4 bpm. The raw HR indices showed slightly higher
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32 TEs (5.4 to 6.4 bpm) than the relative HRR indices (3.0 to 4.0 bpm) that resulted in higher
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34 MDDs for the raw HR indices. The TE found for the HRR60s (3.0 bpm) was similar to
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36 previously reported by Dupuy et al. (2012) (HRR60s = 4.0 bpm), but is lower than the
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38 reported by Bosquet et al. (2008) (HRR60s = 10.3 bpm). Differences in the recovery
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40 protocols might explain such divergence as previously recovery consisted of 1 minute in
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42 the standing position (Bosquet et al., 2008) that likely resulted in varied absolute changes in
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44 HR leading to a greater TE. In contrast the current study employed a supine recovery period
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46 that likely resulted in more stable and reliable changes in HR and smaller TE. The
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48 determination of these agreement parameters has important implications. TE is employed
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50 for estimating sample sizes required in clinical studies, while MDD represents the minimal
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52 difference necessary between repeated tests to consider a real change when evaluating
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4 individual responses to interventions (de Vet et al., 2006). Thus, the specific TE and MDD
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6 determined here for each HRR index should be considered in research and clinical settings
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8 involving HRR evaluation in patients with IC.
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11 When agreement was indicated by CVs (percentage of their respective means),
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13 higher CVs were obtained for relative HRR indices (8.6 to 45.6%) than for raw HR indices
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15 (4.6 to 7.2%). A similar pattern has been previously reported in healthy subjects (Bosquet
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17 et al., 2008; Tulumen et al., 2011; Boulosa et al., 2014) and may reflect a calculation
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19 limitation of the measures with the raw HR indices likely to be similar in terms of absolute
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21 HR values for the calculation of CV (i.e. numerator and denominator values were similar to
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23 each other and hence, smaller CV). In comparison, the HRR indices were calculated from
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25 changes in absolute HR with these smaller mean values impacting the calculation of CV to
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27 a greater extent. It is important to note that all CVs, except for HRR30s, were acceptable,
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29 and can be interpreted as good agreement. The higher CV for HRR30s might be related to
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31 the predominance of parasympathetic reactivation in this early phase of recovery (Imai et
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33 al., 1994) and variable decline in HR. Similarly, Boulosa et al. (2014) also reported a high
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35 CV for HRR30 (22.6%) in healthy individuals with this value approximately half that of the
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37 current study. The greater CV for HRR30s in the current study may indicate variable
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39 parasympathetic reactivation for patients with IC as a result of their disease and/or
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41 progression. Therefore, the use of latter HRR indices may be more reliable and appropriate
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43 for this clinical population.
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52 Collectively, the absence of systematic bias, the excellent reliability and the good
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54 agreement for most of the raw HR and relative HRR indices demonstrated that HRR was
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56 highly reproducible in patients with IC. As high reproducibility of these indices has also
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4 been previously reported in healthy subjects (Buchheit et al., 2008; Arduini et al., 2011;
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6 Tulumen et al., 2011; Boulosa et al., 2014), the current results indicate that patients with
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8 IC does not present impaired HRR reproducibility.
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12 It was interesting to observe that the HRR indices that are mainly used for clinical
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14 evaluation of HRR and cardiovascular risk, HRR60s, HRR120s and HRR300s (Peçanha et
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16 al., 2014) showed excellent reliability (ICCs ≥ 0.879) and good agreements (TEs ≤ 4.0
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18 bpm) in the current study. However, as stated before, some concern is raised regarding the
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20 employment of HRR30s in clinical settings and research with patients with IC since it
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22 presented high reliability (ICC =0.781) but poor agreement (TE = 3.7, MDD = 10.4 and CV
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24 = 45.6). Thus, the present results suggest that HRR60s, HRR120s and HRR300s might be
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26 better indices for evaluating HRR in patients with IC.
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31 While the current study identified novel findings for HRR reproducibility in a
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33 clinical population, the results should be cautiously. The current study examined patients
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35 with IC that were well familiarized with the maximal graded exercise test, which might
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37 have contributed to more reproducible results (Gardner et al., 1991). Secondly, the current
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39 study only included men, which limits the extrapolation of its results to women who should
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41 be studied in the future. Thirdly, the patients were not in use of medications that directly
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43 affected HR responses to exercise. Lastly, it is still not known if the present results are
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45 applicable to other exercise protocols. Patients with other characteristics, using other
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47 medications and submitted to other exercise protocols should be investigated by future
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49 studies. However, it is import to highlight that by our knowledge, the current study is the
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51 first to document the reproducibility of HRR in patients with IC.
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Conclusion

The vast majority of raw HR and relative HRR indices following maximal graded exercise were highly reproducible in male patients with IC. Therefore, these indices may be used in research and clinical settings with this population for assessing differences between individuals and effects of interventions on the integrity of autonomic cardiac function and on cardiovascular risk.

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CONFLICT OF INTEREST

The authors have no conflicts of interest

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Table 1. Clinical characteristics of patients with intermittent claudication (n=19).

Characteristic	Value
Age (ys)	64 ± 8
Height (m)	1.68 ± 0.06
Weight (kg)	74.4 ± 11.6
Body mass index (kg/m ²)	26.4 ± 3.6
Ankle brachial index	0.58 ± 0.15
Cardiovascular Risk Factors and Comorbidities Conditions	
Obesity, n (%)	4 (21.1)
Hypertension, n (%)	17 (89.5)
Dyslipidemia, n (%)	18 (94.7)
Diabetes mellitus, n (%)	6 (31.6)
Current smokers, n (%)	7 (36.8)
Heart disease, n (%)	1 (5.3)
Stroke, n (%)	3 (15.8)
History of neoplasm, n (%)	3 (15.8)
Drug therapy	
Aspirin, n (%)	17 (.89.5)
Statin, n (%)	17 (89.5)
Angiotensin-converting enzyme inhibitor or receptor blocker, n (%)	12 (63.2)
Diuretics, n (%)	9 (47.4)
Dihydropyridine calcium channel antagonist, n (%)	6 (31.6)
Oral hypoglycemic, n (%)	5 (26.3)

Continuous variables are expressed as mean ± SD. Obesity defined as body mass index ≥ 30 kg/m². Hypertension, dyslipidemia and diabetes mellitus were self-reported by the subjects.

Table 2. Test duration, total walked distance, raw heart rate (HR) and relative heart rate recovery (HRR) indices measured in test and retest treadmill exercise tests in patients with intermittent claudication (n=19).

Variable	Test 1	Test 2	Difference	P-value
Test				
Test duration, s	780 ± 425	793 ± 445	-13 ± 86	0.520
Total walked distance, m	656 ± 318	665 ± 338	-8 ± 84	0.666
Raw HR indices, bpm				
Peak HR	126.4 ± 14.2	122.5 ± 13.1	3.9 ± 8.3	0.056
HR30s	117.8 ± 15.9	114.6 ± 15.6	3.2 ± 7.6	0.083
HR60s	104.0 ± 12.7	100.1 ± 13.1	3.9 ± 8.4	0.057
HR120s	93.9 ± 13.4	89.1 ± 13.9	4.8 ± 9.1	0.032*
HR180s ^a	90.3 ± 10.9	87.8 ± 12.0	2.5 ± 9.0	0.253
HR240s	88.8 ± 11.9	85.2 ± 11.2	3.6 ± 8.8	0.089
HR300s	86.6 ± 11.5	83.7 ± 10.3	2.9 ± 7.6	0.114
Relative HRR indices, bpm				
HRR30s	8.5 ± 6.8	7.8 ± 5.6	0.7 ± 5.3	0.579
HRR60s	22.4 ± 7.1	22.4 ± 7.8	0.0 ± 4.2	1.000
HRR120s	32.5 ± 7.9	33.4 ± 9.3	-0.9 ± 5.7	0.476
HRR180s ^a	36.2 ± 9.8	34.9 ± 8.1	1.2 ± 4.7	0.289
HRR240s	37.5 ± 9.0	37.3 ± 9.0	0.3 ± 5.6	0.839
HRR300s	39.8 ± 9.3	38.8 ± 8.8	1.0 ± 4.8	0.374

Values are mean ± SD. HR = heart rate; HRR = heart rate recovery. ^an=18, due to technical issues. *p < 0.05

Table 3. Reproducibility data of raw heart rate (HR) and relative heart rate recovery (HRR) indices after treadmill exercise tests in patients with intermittent claudication (n=19).

Variable	ICC	TE (bpm)	CV (%)	MDD (bpm)
Raw HR indices				
Peak HR	0.898	5.9	4.7	16.3
HR30s	0.938	5.4	4.6	14.9
HR60s	0.883	5.9	5.8	16.4
HR120s	0.875	6.4	7.0	17.8
HR180s ^a	0.820	6.3	7.1	17.6
HR240s	0.831	6.2	7.2	17.3
HR300s	0.853	5.4	6.3	14.9
Relative HRR indices				
HRR30s	0.781	3.7	45.6	10.4
HRR60s	0.915	3.0	13.2	8.2
HRR120s	0.879	4.0	12.2	11.1
HRR180s ^a	0.926	3.3	9.4	9.3
HRR240s	0.831	3.9	10.5	10.9
HRR300s	0.925	3.4	8.6	9.4

Values are mean \pm SD. ICC = intraclass correlation coefficient; TE = typical error; MDD = minimal detectable difference; CV = coefficient of variation. ^an=18, due to technical issues

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Figure Legends

Figure 1 – Bland & Altman plots (systematic bias \pm limits of agreement) for individual values of raw heart rate (HR) indices measured in test and retest treadmill exercise in patients with intermittent claudication.

Figure 2 - Bland & Altman plots (systematic bias \pm limits of agreement) for individual values of relative heart rate recovery (HRR) indices measured in test and retest treadmill exercise in patients with intermittent claudication.

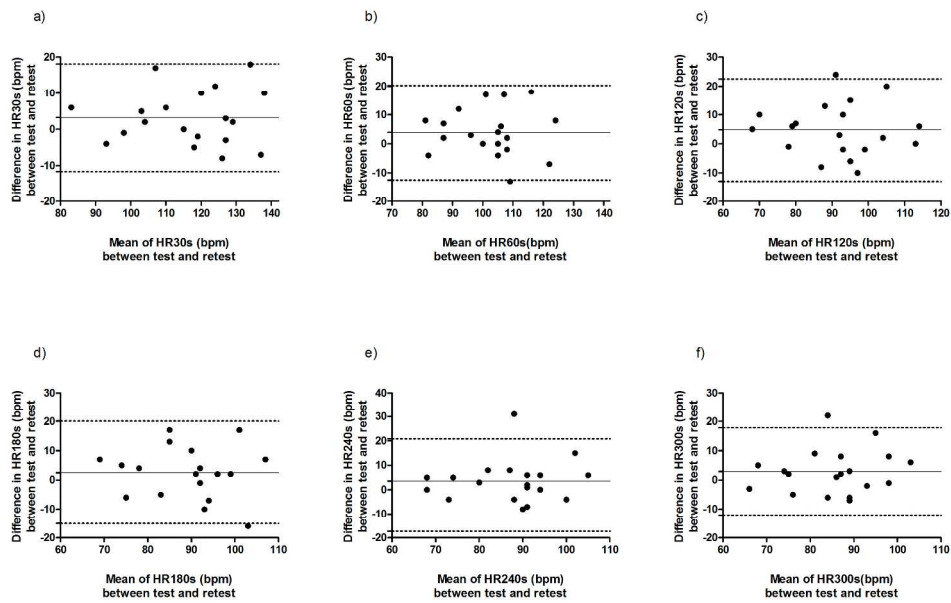


Figure 1. Bland & Altman plots (systematic bias \pm limits of agreement) for individual values of raw heart rate (HR) indices measured in test and retest treadmill exercise in patients with intermittent claudication.

268x171mm (300 x 300 DPI)

Review

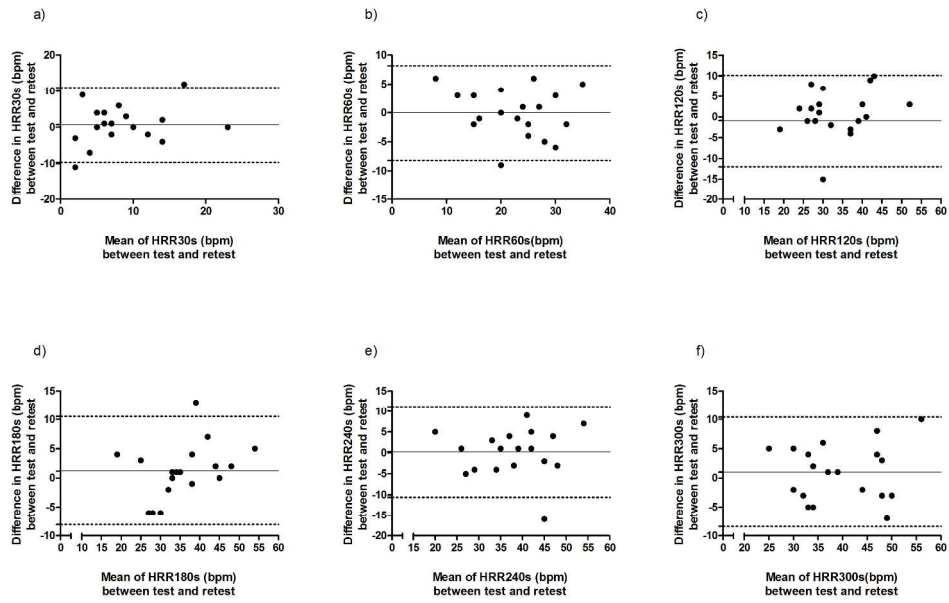


Figure 2. Bland & Altman plots (systematic bias \pm limits of agreement) for individual values of relative heart rate recovery (HRR) indices measured in test and retest treadmill exercise in patients with intermittent claudication.

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