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Reproducibility of Heart Rate Recovery in Individuals with Low Heart Rate Recovery Response

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Abstract

Objective: To examine the reproducibility of HRR in healthy individuals with slow HRR response undergoing routine annual checkups. **Method:** HRR data (>18 b/min; Group 1 and <> 18 b/min; Group 2) were analyzed using a fixed-effects regression model adjusted for age and gender, including random effects group-specific slopes on age. **Results:** One hundred and thirteen individuals (56.5 ± 9.2 y), underwent 573 cumulative ESTs with an average of 5.1 ± 1.6 tests per individual during a 21-year retrospective follow-up. No differences were found in anthropometric measurements and blood variables. All individuals achieved 94% ± 7.7% of age-predicted HR max at peak EST. Group 2 demonstrated 38% of inconsistent HRR. Regression analysis demonstrated a decrease of 0.5 b/min, on average across individuals, in HRR per each extra year of age. The random effects showed an inter-subject SD level of 9.91 b/min and an SD on the age slope of 0.40 b/min/year. **Conclusion:** HRR showed low reproducibility in nearly 40% of tests, which was not reflected by the variation of HR nor in the slope of age during a 21-year retrospective follow-up.

Keywords

Retrospective Analysis, Exercise Stress Test, Healthy Individuals, Fluctuated Heart Rate Recovery

1. Introduction

HR recovery (HRR) is defined as the difference in HR from peak exercise stress test (EST) to that recorded 1 minute during recovery. A fast decrease in HR of >18 b/min during the active recovery period reflects normal recovery response [1] [2], while a reduction of less than 18 b/min is regarded as an abnormal/slow response [3] [4]. Several studies investigated the changes in HRR following ESTs and found a positive relationship with cardiorespiratory fitness level [5] [6], exercise training [7], and cardiac rehabilitation [8], and an inverse relationship with cardiovascular mortality [9]. We [10] have previously reported that 20 patients who demonstrated HRR below 18 b/min were recruited to perform a second EST within three months. Thirteen of the 20 patients (65%) showed HRR above 18 b/min in the subsequent EST, and only seven patients (35%) remained with HRR below 18 b/min [10]. Therefore, our purpose in the current study was to assess the reproducibility of HRR following multiple ESTs. Previous studies have shown high reproducibility of HRR during short-term follow-up between tests with a low variation and no significant differences between ESTs. [11] [12]. Similar results were demonstrated in long-term studies [13] [14] [15], with no significant differences between ESTs.

In contrast, other studies have shown a low reproducibility of HRR in short- or long-term follow-ups [16] [17]. These complex HRR reports emphasized the importance of investigating the changes of HRR in long-term repeated ESTs. Therefore, our current study examined the reproducibility of HRR in middle-aged apparently healthy individuals undergoing routine annual checkups during a 21-year retrospective follow-up.

2. Method

The study was conducted at the Medical Screening Unit, Sheba Medical Centre, on healthy middle-aged individuals undergoing repeated ESTs during annual checkups over a 21-year of retrospective follow-up. The local IRB Committee approved the study protocol (approval No. SMC-7602-09). Inclusion criteria included healthy individuals with no medical treatments or clinical needs that previously underwent at least 3 ESTs as part of their routine annual employee screening check-ups and included the following: anthropometric characteristics (weight (kg), height (cm), and BMI (kg/cm^2)), blood and lipids profile (including Hemoglobin (g/dL), red blood cells (g/dL), total cholesterol (mg/dL), LDL cholesterol (mg/dL), HDL cholesterol (mg/dL), and triglycerides (mg/dL). EST parameters include resting systolic blood pressure (SBP mmHg) and diastolic blood pressure (DBP mmHg), resting HR (b/min), target maximum HR achieved by age-predicted (%, THR), metabolic equivalent of task (MET, 1 MET equals 3.5 mL of oxygen/kg/min), peak exercise SBP (mmHg), and DBP (mmHg), peak HR (b/min), HR recovery at 1 minute (HRR, b/min), and the difference in HRR from peak exercise (b/min). All participants are interviewed at the time of each annual examination using standard questionnaires that gather information about demographic characteristics, medical history, and health-related habits, including regular physical activity (on a yes/no basis).

Data were collected from the Medical Screening Unit archive between 1993 and 2014, reflecting 21 years of retrospective follow-up. HRR data were documented manually directly from the electrocardiographic charts. We looked for HRR values above 18 b/min or lower. For that, we took medical files from the Medical Screening Unit archive and documented the HRR from each of the ESTs, for each individual. These tests (within a specific file) could be categorized either as "high HRR response"; individuals having HRR constantly above 18 b/min in all ESTs (Group 1) or "low HRR response"; individuals having HRR above 18 b/min in some ESTs and below 18 b/min in other ESTs (Group 2). We stopped collecting data after reaching an arbitrary number of 136 individuals. Twenty-three (23) individuals were excluded from the analysis due to not meeting at least one of the following four criteria: 1) had less than 3 ESTs; 2) above the age of 75; 3) HRR constantly below 18 b/min in all ESTs; 4) use of bicycle ergometer (see **Figure 1** for details).

All ESTs described in the current study were performed uniformly on a running treadmill using the Bruce protocol.

All individuals achieved maximal EST (age-predicted HR max) and were free of arrhythmia or other exercise limitations before, during, and after all ESTs. There were no incidents or medical complications such as clinical symptoms (chest pain, hypotension, hypertension, etc.), ECG changes associated with myocardial ischemia (>1.0 mm ST-segment depression, ST-segment elevation), or ventricular arrhythmia fatigue, or dyspnea.

The data were organized using Microsoft Excel 2018, and statistical analyses were performed using SPSS statistical software (version 25), R (version 3.5.2), and Prism (version 9) Graph-Pad Software. Anthropometric characteristics, SBP, DBP, and blood and lipids profile were calculated as an individual's mean during the 21-years follow-up and were statistically compared between groups using parametric t-test or nonparametric, Mann-Whitney test, according to D'Agostino & Pearson omnibus normality test. We analyzed the reproducibility of HRR between the two groups (Group 1 and Group 2) by fitting a mixed-effects

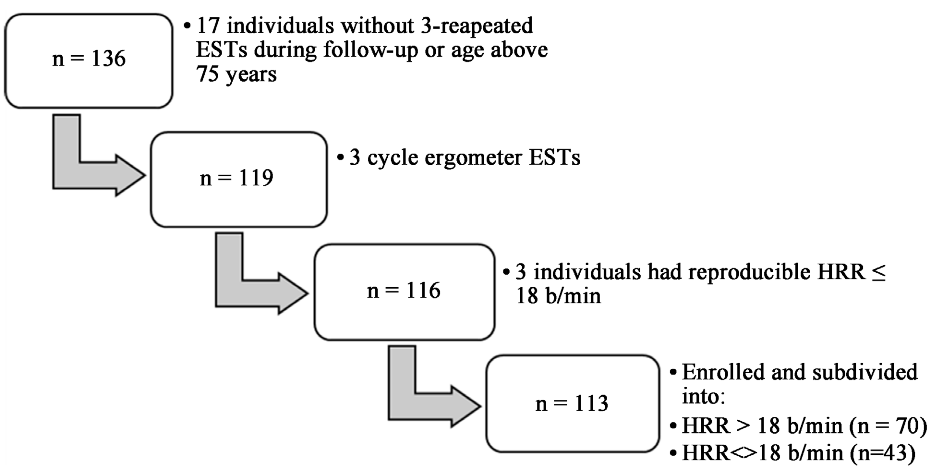

Figure 1. Flow chart demonstrating the number of individuals enrolled in the study.

regression model to the BP and HR at rest, at peak exercise, and 1-minute during recovery. These models included fixed effects for age and gender and random effects for the intercepts and the slopes on age. For the overall comparison of the study groups, each individual's age is summarized by the average age at which tests were run. Data are presented as mean ± SD, calculated by the summary of summaries approach methods, with a p-value of ≤0.05 considered significant.

3. Results

One hundred and thirteen individuals (56.5 ± 9.2 years old) underwent a total of 573 cumulative ESTs with an average of 5.1 ± 1.6 tests per individual (ranging between 3 - 10 tests) over 21 years of retrospective follow-up. Seventy individuals (62%, Group 1) obtained 335 of 573 ESTs (58.5%), demonstrated high consistency of HRR > 18 b/min between ETSs (54.0 ± 9.0 years old) and 43 individuals (38%, Group 2) obtained 238 of 573 ESTs (41.5%), demonstrated low HRR response between ESTs (60.3 ± 8.0 years old) with a significant age difference between groups, $p < 0.001$.

No significant differences were found in all anthropometric measurements, lipids profile, and resting blood pressure between groups, adjusted for age and gender. All of these results were within the normal range during the 21-year follow-up (**Table 1**).

Although a significant difference of 5.1 b/min in the total average of resting HR between the two groups ($p = 0.005$) was found, the fixed effects regression shows almost no change with age (a drop of 0.05 b/min for each year with similar slopes for each group) and no significant difference between men and women. The random effects of the resting HR, show "within-subject" errors with an SD of 8.15 b/min, inter-subject SD of 7.67 b/min (slightly smaller than the within SD), and an SD on the age slope of 0.31 b/min/year. The inter-subject SD for the slope suggests considerable variation in the slope from one subject to another, some with positive slopes and others negative.

All individuals reached a total average peak HR of 94.2% ± 7.0% of age-predicted maximum HR at peak EST with peak MET's of 11.9 ± 2.1 METs (for both groups). The fixed effects show a significant decrease of peak HR with age (0.95 b/min per year), with non-significant differences of 3.4 b/min between the two groups and 1.17 b/min between men and women. Furthermore, the random effects, of the peak HR, show "within-subject" errors with an SD of 6.60 b/min and an inter-subject SD of 9.7 b/min (larger than the within SD). The inter-subject SD for the slope on age was 0.45 b/min/year, which implies that the subjects typically have negative slopes, with (at the extremes) some close to 0 and others of about −1.85.

The differences in HRR in Group 2 varied between 2 b/min to 57 b/min, meaning that HRR in some ESTs is below 18 b/min and during other ESTs; HRR is above 18 b/min, for the same individual, during a 21-year retrospective follow up. While in Group 1, HRR was constantly above 18 b/min, the values varied between 19 b/min and 83 b/min with an SD of 8.6 b/min (adjusting for age), similar to the SD in Group 2 (10.8 b/min), which both represent low reproducibility of ESTs during the 21-year follow-up (Figure 2).

Table 1. General characteristics over 21-years follow-up.

Variables:	HHR > 18 b/min (Group 1) n = 70 (73% male)	HRR <> 18 b/min (Group 2) n = 43 (88% male)	p-value
Age (years)	54.0 ± 9.0	60.3 ± 8.0	***p < 0.001**
Weight (kg)	79.5 ± 15.9	82.7 ± 14.2	p = 0.38
Height (cm)	174.3 ± 8.1	174.8 ± 8.5	p = 0.93
BMI (kg/cm^2)	26.0 ± 3.8	26.9 ± 3.6	p = 0.41
Blood pressure			
Resting SBP (mmHg)	120.4 ± 12.2	125.6 ± 13.8	p = 0.79
Resting DBP (mmHg)	77.1 ± 6.2	78.8 ± 5.5	p = 0.66
Blood lipids profile			
Triglycerides (mg/dL)	113.4 ± 44.5 (n = 64)	130.0 ± 62.1 (n = 41)	p = 0.11
Total Cholesterol (mg/dL)	182.4 ± 24.3 (n = 64)	182.0 ± 24.1 (n = 41)	p = 0.93
LDLCholesterol (mg/dL)	114.0 ± 21.2 (n = 64)	113.2 ± 20.5 (n = 41)	p = 0.84
HDL Cholesterol (mg/dL)	48.0 ± 8.9 (n = 64)	47.4 ± 10.4 (n = 41)	p = 0.46

Individual's mean characteristics during the 21-years follow-up ("summary of summaries" approach). HHR > 18 b/min (Group 1), HRR <> 18 b/min (Group 2). All variables in the first part of the table were statistically compared between groups using the t-test (for age, total cholesterol, and LDL) or the nonparametric, Mann-Whitney test (for weight, height, BMI, resting DBP, HDL, and TG), according to D'Agostino & Pearson omnibus normality test. The blood pressure data were compared using a mixed-effects regression model adjusted for age and sex, with random intercepts and random slopes for age.

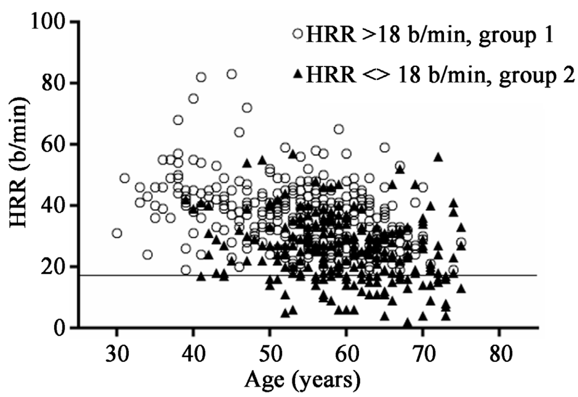

Figure 2. Changes of the individual HRR (b/min) with age (years) during a 21-year follow-up. Circles represent HRR > 18 b/min; Group 1, and triangles represent the inconsistent HRR, above and below 18 b/min; Group 2. The thin horizontal line represents 18 b/min. HRR; heart rate recovery measured at one-minute post-peak exercise stress test (EST).

The fixed effects show a significant slope of HRR on age (a drop of 0.50 b/min for each year in age). Thus, for individuals who differ in age by 20 years, the average difference in HRR would be 10.0 b/min. There were non-significant differences of 3.37 b/min between the two groups and 4.02 b/min between men and women.

The random-effects show "within-subject" errors with an SD of 9.59 b/min, an inter-subject SD of 9.91 b/min (slightly larger than the within SD), and an SD on the age slope of 0.40 b/min/year. The latter is considerable, given that the typical slope is −0.50 b/min/year. Therefore, some subjects had much steeper decreases, and others increased over time. The overall slope of −0.50 is still very significant ($p < 0.0001$), even after considering this inter-subject variability in slope. Moreover, a model including an interaction between group and age showed no evidence that the slopes differed by group. It should be pointed out that subject averages fall on a continuum with no clear demarcation line between them.

Figure 3 emphasizes the large "within-subject" spread, showing that many of the subjects "near the middle" (in terms of average HRR) have at least one reading below 18 b/min, reflecting low reproducibility of HRR between tests.

4. Discussion

We investigated the reproducibility of HRR during multiple repeated ESTs of apparently healthy, middle-aged individuals during a 21-years retrospective follow-up. We found that among nearly 40% of individuals, HRR demonstrated low HRR response between ESTs, and these changes stood for themselves and were not explained by within-subject HR variations, age, or gender. It is important to emphasize that our cohort consisted of apparently healthy individuals without known clinical conditions that require any medications during the entire observation period, thus neglecting the possibility that those changes in HRR were associated with the use of beta-blocker medications.

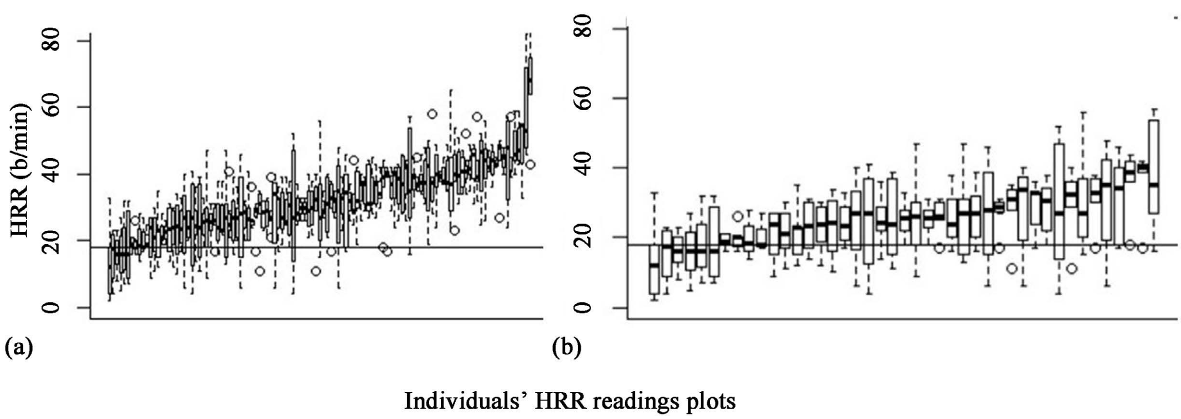

Figure 3. Individuals' HRR readings plots in Groups 1 and 2 (a), and in Group 2 ((b); inconsistent HRR). Individual-specific plots have a "box" extending from their 25th percentile HRR to their 75th percentile and lines from the box to the minimum and the maximum of HRR. The dark lines in the boxes are the medians. When there is an "unusual" value, it is displayed as a separate circle rather than the line's extreme point. The thin horizontal line represents 18 b/min. HRR; heart rate recovery at a one-minute post-exercise.

Our present study motivation was driven from our previous one, where patients suspected of having coronary artery disease showed the inconsistency of HRR among 2/3 of patients undergoing a second EST within three months from the last EST [10]. Our current data demonstrate that HRR is not reproducible and may differ between tests, both in patients suspected of coronary artery disease and apparently healthy individuals. Therefore, our results question the physiological and clinical impacts of HRR measured in a single exercise stress test.

Previous investigations demonstrated high reproducibility of HRR between two repeated ESTs, 1 and 20 years later [18] [19] [20]. In contrast, our current study emphasizes that across both HRR groups, there was a low reproducibility of HRR between ESTs during a 21-year follow-up. In other words, there is a great deal of inter-subject variation above and beyond what is explained by age and gender.

The mixed model regression analysis goes one step further and looks at the extent of variation within a single individual's sequence of measurements. We found that the within-subject SD for those in (Group 2) was 10.8 b/min, which highlights the amount of variation within subjects as even more extensive than the variation between subjects (age and gender-adjusted), and is larger than the typical difference between two individuals whose age differs by 20 years. For those in Group 1 (>18 b/min), the within-subject SD was 8.6 b/min, a bit smaller but equal to the between-subject SD after age and gender adjustments. The very large within-subject SD suggests that a given individual's results can change dramatically from one year to the next. Therefore, we can summarize that HRR has low reproducibility and change between tests in both groups, having a large degree of variation, with within-subject SD over repeat tests of 9.6 b/min, which is at the same level as the inter-subject variation SD of 9.91 b/min.

Study Limitations

First, we did not examine the clinical outcome or calculated the prognostic value of HRR post-EST, since it was not the intention of the present investigation. We focused on whether methodologically HRR is a reproducible value between repeated exercise stress tests or with age. Secondly, data regarding the individual's risk factors and physical activity were collected subjectively, and therefore this data should be taken into consideration.

5. Conclusion

Our results demonstrate that HRR is not a reproducible value and changes between tests in nearly 40% of individuals undergoing routine ESTs over a 21-year retrospective follow-up. The low reproducibility of HRR is not reflected by HR's variation in terms of SD (within-subjects) which showed similar variation in both groups. The interpretation of HRR based on a single exercise stress test should be taken with caution.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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