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Heart Rate Recovery 10 Seconds After Cessation of Exercise Predicts Death
Yordi J. van de Vegte, Bsc; Pim van der Harst, MD, PhD; Niek Verweij, PhD

Background—Heart rate recovery (HRR) is commonly defined as the decrease of heart rate at 1 minute after cessation of exercise and is an important predictor of all-cause mortality and death associated with coronary artery disease. However, HRR at earlier time intervals after cessation has not been well evaluated and might better reflect PNS reactivation. We hypothesize that early HRR indices within the first minute is better associated with all-cause and coronary artery disease mortality compared with HRR at 1 minute.

Methods and Results—The prognostic value of HRR at 10, 20, 30, 40, and 50 seconds after cessation of exercise was investigated in 40 727 selected UK Biobank participants (mean age 56 years, 45% male) free from cardiovascular disease. During a median follow-up period of 6 years, 536 participants died (including 39 of coronary artery disease). In multivariable analyses, including adjustments for aerobic exercise capacity, cardiovascular risk factors, and factors associated with mortality in general, only HRR at 10 seconds remained predictive of both all-cause and coronary artery disease mortality. Effects of HRR were larger and more significant when measured early after exercise cessation. Moreover, the association of change in heart rate between 10 seconds and 1 minute after exercise cessation with mortality was dependent on HRR at 10 seconds.

Conclusions—We provide evidence that decreased HRR at 10 seconds after cessation of exercise is a superior predictor of outcome compared with HRR at later time intervals. This observation might have important implications for the future reporting and interpretation of exercise tests. (J Am Heart Assoc. 2018;7:e008341. DOI: 10.1161/JAHA.117.008341.)

Key Words: autonomic nervous system • exercise testing • heart rate recovery • mortality

Heart rate recovery (HRR), the decrease of heart rate following cessation of exercise, has been previously investigated and has been established as a predictor of coronary artery disease (CAD),1,2 death from CAD,3 and cardiovascular,4 noncardiovascular,5 all-cause mortality.1,3,6,7 Some of these studies have been conducted in a population without a history of cardiovascular disease1,3,5,6 and others in symptomatic patients who were referred for an exercise test.1,4,7

HRR is thought to reflect the balance of reactivation of the parasympathetic nervous system (PNS), withdrawal of the sympathetic nervous system, and possibly circulating catecholamines. It has long been known that reactivation of the PNS is the main contributor to interindividual HRR differences and that the effect of this reactivation is strongest in the first 30 seconds after termination of exercise.3 Despite this knowledge, HRR is commonly determined at 1 minute after termination of exercise.1,3,6 Recently, a study by McCrory et al9 described HRR within a 1-minute interval after an orthostatic challenge, and found that speed of HRR in the immediate 20 seconds was the strongest predictor of all-cause mortality. Whether HRR measured early after exercise cessation is also of increased value for prediction models remains to be determined.

We hypothesized that HRR is more predictive of mortality when measured early after exercise cessation, as this might better reflect PNS reactivation. The purpose of this work was therefore to systematically study HRR at multiple time intervals after cessation of exercise as predictors of mortality.

Methods
The data, analytic methods, and study materials beyond what is described in this article will be made available by the...
Clinical Perspective

What Is New?

• The value of heart rate recovery to predict mortality is greatest when measured at 10 seconds after cessation of exercise, compared with measurements of heart rate recovery at later time points up to 1 minute.
• These results are consistent with the theory that the underlying pathophysiology linking heart rate recovery with mortality may be caused by parasympathetic reactivation, which is greatest within the first 30 seconds of exercise.

What Are the Clinical Implications?

• From a clinical perspective, these findings could be taken into consideration for the interpretation of exercise testing or in the application of wearable health devices.

Analysis of Exercise ECGs and Quality Control

Exercise ECG data were provided by the UK Biobank in bulk format as an XML file per test. We used gQRS to detect QRS waves\textsuperscript{13} followed by detection of individual QRS peaks by the Construc\textsuperscript{14} algorithm. Reliable RR intervals were obtained following the international guidelines from the Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology.\textsuperscript{15} Abnormal RR interval values of RR <0.286 or RR >2 seconds, corresponding to a heart rate slower than 30 beats per minute or faster than 210 beats per minute, were discarded.\textsuperscript{15} Further data cleaning of abnormal RR intervals was performed according to Chen and Liu’s method\textsuperscript{16} for automatic detection of outliers in time series by interpolation, incorporated in the “isclean” function of R package “forecast v7.3”. A total of 2498 exercise ECGs were excluded for excess noise. To detect noise ECGs, we determined the SD over a moving SD, with a window length of 3 beats, of all RR intervals per ECG per phase. An SD of near 0 suggests little to no noise in the RR detection. The median SD among all exercise ECGs was 0.0065, an extreme value of >0.05—98th percentile—was considered to be noise and confirmed by manual inspection of the RR interval signals. Next, HRR was calculated by the difference in maximum heart rate achieved during exercise and mean heart rate at 10 seconds after exercise. Finally, participants with an extreme HRR (more than ±5 SD from the mean) were excluded on a per phenotype basis. Further descriptions and the source code of the methods, including an example, are available at https://github.com/niekverw/E-ECG.
Predictive Value of Heart Rate Recovery

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Primary End Points

Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre and the NHS Central Register Scotland for participants from England and Wales and participants from Scotland, respectively. The cause of death was defined according to the ninth and tenth revisions of the ICD together with self-reported events. CAD was defined as myocardial infarction (ICD-10 codes I21, I22, I23; ICD-9 code 410) or other ischemic heart disease (ICD-10 codes I24, I25, Z955; ICD-9 code 414).

Statistical Models

All variables were collected during the individuals' first visit at one of the UK Biobank centers. Age, sex, body mass index (BMI), systolic blood pressure, resting heart rate, duration of the exercise test, exercise capacity, and the Townsend deprivation index were treated as continuous variables. The Townsend deprivation index is a measure of material deprivation within a population based on unemployment, noncar ownership, nonhome ownership, and household overcrowding. The Townsend deprivation index was skewed in our sample of the UK Biobank and therefore we single-inverse normalized this variable, in line with previous research. History of disease and medication were treated as binary variables, including diabetes mellitus, cancer, lung disease, family history of cardiovascular disease, and high blood levels of lipids as well individual self-reported usage of diuretics, β-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors during the nurse interview. Hyperlipidemia was defined as any disorder of lipoprotein metabolism and other lipemias according to ICD-10 code E78. Smoking status was defined as ideal (never smoked or quit ≥12 months ago), intermediate (quit smoking ≤12 months ago), or poor (current smoker). Current physical activity was based on questionnaires concerning do-it-yourself and exercise activities using current guidelines for ideal cardiovascular health. Ideal physical activity was defined as either ≥150 minutes per week of moderate intensity or ≥75 minutes per week of vigorous intensity or ≥150 minutes per week of moderate plus vigorous intensity. Poor physical activity was defined as no physical activity at all, while intermediate physical activity was defined as anything in between. Covariates were selected based on previous studies of HRR and also on the relationship of variables in the UK Biobank potentially related with HRR or mortality, and which were significantly associated with HRR (P<0.01) after age and sex adjustments (eg, blood cell parameters or maximum heart rate).

Four Cox regression models were used to systematically study the predictive value of HRR on mortality at multiple time intervals: (1) a univariable model; (2) a multivariate model correcting for the known confounders including age, sex, BMI, and exercise capacity; (3) an extended multivariate model based on previous studies on HRR after exercise with traditional cardiovascular risk factors that included age, sex, BMI, exercise capacity, exercise duration, systolic blood pressure, diabetes mellitus, hyperlipidemia, smoking behavior, current physical activity behavior, and a family history of cardiovascular disease; and (4) another extended multivariate model to adjust for risk factors associated with all-cause mortality as well, including age; sex; BMI; exercise capacity; exercise duration; systolic blood pressure; hyperlipidemia; use of diuretics, β-blockers, calcium channel blockers, or angiotensin-converting enzyme inhibitors; ever receiving a doctor diagnosis of cancer, lung disease, or diabetes mellitus; smoking behavior; physical activity behavior; a family history of cardiovascular disease; the Townsend deprivation index; and resting heart rate.

All statistical analyses were performed in Stata/SE 14 (StataCorp). Hazards ratios (HRs) and corresponding 95% confidence intervals (CIs) for each primary outcome were estimated in separate Cox proportional hazard models. Schoenfeld residuals were calculated and found significant if the P value of the Schoenfeld test exceeded 0.05. Residual plots were visually inspected in case of a significant Schoenfeld test to assess whether it was caused by the large sample size, known to bias the test statistics, or a violation of the proportionality assumption. Phenotypes of HRR were standardized to a mean of 0 and SD of 1 to allow for comparisons between the different HRR measurements.

Results

A total of 40 727 participants were included in this study who met our criteria of cycling at 50% of the maximum workload, completing the full course of exercise (including 50 seconds of recovery) and having a cardiovascular disease–free history. The cohort was on average aged 56 years, consisted of 45% of men and cycled on average for 428 seconds at an exercise capacity of 88 watts. Detailed baseline characteristics and descriptive statistics of the participants are depicted in Table 1. There were no differences between those included in the current study compared with the individuals without analyzable ECGs (P>0.05). After a median follow-up of 5.8 (range 5.5–6.1) years, 536 died of all causes and 39 of CAD. Compared with the surviving study population, deceased participants were older, more likely male, and had higher levels of BMI, systolic blood pressure, and comorbidities.

HRR as a Predictor of Mortality

The association between HRR and all-cause and CAD mortality are presented in Table 2. HRR was associated with all-cause and CAD mortality in the univariate Cox regression analyses.

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ORIGINAL RESEARCH
HRR in the early phase after exercise cessation was a stronger predictor of mortality, compared with HRR measured at later time points. In multivariate analysis, HRR remained predictive of all-cause mortality after correction for cardiovascular risk factors (model 2 and 3). In multivariate analyses, in which we corrected for both traditional cardiovascular risk factors and Townsend deprivation index, HRR remained predictive of all-cause mortality.
The predictive value of HRR on CAD mortality follows the same trend as all-cause mortality. All univariate associations were significant, with lower HRs and P values early after cessation of exercise across all models. Only HRR10 remained predictive of CAD mortality after multivariable correction. The proportionality assumptions of all multivariable Cox regression models were satisfied.

Since HRR10 was the strongest predictor for mortality of all HRR variables in the multivariate models, we wondered whether the association between HRR and mortality was fully explained by the first 10 seconds, and not by the change in heart rate between 10 seconds and 1 minute. For this, a multivariate Cox regression model was fitted with both HRR10 and HRR10 to 50 seconds (the subtraction of HRR10 from HRR50) in one model, correcting for basic risk factors (model 2). HRR10 was strongly associated with all-cause (HR, 0.757; CI, 0.683–0.839 [P=1.1×10^{-07}]) and CAD (HR, 0.506; CI,
0.328–0.779 \([P=2.0 \times 10^{-03}]\) mortality, in contrast to HRR10–50 seconds (HR, 0.989, CI, 0.898–1.090 \([P=0.82]\) and HR, 1.068; CI, 0.746–1.529 \([P=0.72]\) respectively). This further indicates that the relationship between HRR and mortality may be originating from heart rate decline in the first few seconds after exercise cessation.

**Sensitivity Analyses**

Sensitivity analyses were performed by adding additional variables to model 4 in order to examine whether the results were also independent of: (1) maximum heart rate, which is also an important exercise ECG marker that is thought to reflect autonomic (dis)balance, is highly related to HRR and has been found to be a predictor of all-cause and CAD mortality in the general population\(^3,21\); and (2) blood cell counts (erythrocytes and leucocytes), as blood cell counts were found to be significantly correlated with HRR \((r^2=0.12–0.22, P<1.0 \times 10^{-18})\). Adjustments for these variables did not attenuate our results (Table S1).

**Discussion**

The major finding of our study is that in all multivariable models, HRR was most strongly associated with death when measured early, at 10 seconds after exercise cessation, compared with HRR measured at later time points.

The hypothesis linking HRR to mortality arose in 1992 from the work that associated components of the autonomic nervous system with sudden cardiac death.\(^22\) Since then, studies have been linking HRR to mortality and have focused on heart rate measured at predefined points of 1 minute after exercise cessation.\(^1,3,6\) However, before these studies were conducted, the belief was that PNS reactivation may have been one of the differentiating factors between a low and high HRR as it has been found to be the strongest influence on HRR in the first 30 seconds after cessation of exercise.\(^8\) PNS reactivation during the early resting phase is thought to be solely mediated by changes in response to the activity in arterial baroreceptors.\(^23\) A recent study of McCrory et al\(^9\) took these findings into a clinical setting by studying the predictive value of HRR after a standing challenge, in which the primary physiological event of interest was the changing activity of the arterial baroreceptors, strengthening our hypothesis that HRR after termination of exercise may be more important immediately after exercise. Compared with McCrory’s study, we studied HRR changes after exercise cessation, which is a more complex physiological state in which sympathetic nervous system activity and circulating catecholamines are still high, making a one-to-one comparison difficult. In line with McCrory’s findings, we provided evidence that HRR should be obtained earlier after exercise.

This finding may be important to consider when bringing HRR into clinical practice or considering it as a measure of fitness. We also suggest a future application for these findings in self-monitoring of heart rate and heart rate–dependent variables, in consideration of the current growing market of wearables\(^24,25\) and the increasing amount of evidence of the accuracy of the heart rate measurement of wearables.\(^26,27\)

**Study Strengths**

The strengths of this study are, first, that it is population based, representing the single largest study of ECG changes to exercise in individuals free from disease to date. Second, the availability of the raw ECG data allowed for measurements of single RR intervals, enabling a series of quality-control steps on a beat-to-beat level that resulted in a high-resolution data set of heart rate profile during exercise. Third, we were able to control for a large range of variables that could potentially confound analyses, facilitated by the detailed characterization of the exercise test itself, availability of high quality hospital record data, baseline measurements, and questionnaires.

**Study Limitations**

Some limitations in our study should be considered. Our study had a relatively short follow-up time compared with previous studies.\(^1,3\) Whereas this is, by far, the single largest study of HRR after exercise in the general population to date (40 727 individuals), there were only 541 (1.32%) individuals who died within a median period of 5.8 years, compared with those in the Framingham Heart Study\(^1\) (n=2967, 5.6% deaths), the Lipid Research Clinics Prevalence Study\(^6\) (n=5234, 5.96% deaths), and the Paris Prospective Study\(^3\) (n=5713, 26.54% deaths). Furthermore, our study was not able to address causality. It is unclear whether the observed effects on mortality are causal or a consequence of an underlying disease. Regardless of this, the results emphasize the importance of HRR to be measured more closely after exercise cessation for its potential use in prediction models. This study was designed to replicate the effect of HRR on mortality and to obtain insights into the relationship between the time of HRR measurement and mortality, which is a fundamental step towards a better understanding of HRR’s pathophysiology.

**Conclusions**

We present novel data linking HRR to all-cause and CAD mortality and provide the first evidence that HRR measured early (10 seconds) after cessation of submaximal exercise is a superior predictor of outcome compared with HRR at
1 minute. This observation has important implications for the future interpretation and reporting of HRR after exercise tests.

Acknowledgments

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Disclosures

None.

References

SUPPLEMENTAL MATERIAL
Table S1. Sensitivity analysis in which the following variables were added to model 4: (a) Maximum heart rate (b) Blood cell counts (erythrocytes and leucocytes).

<table>
<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
<th>CAD mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>HRR10</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4a</td>
<td>0.782 (0.698 - 0.875)</td>
<td>2.0×10^{-5}</td>
</tr>
<tr>
<td>Model 4b</td>
<td>0.801 (0.713 - 0.900)</td>
<td>2.0×10^{-4}</td>
</tr>
<tr>
<td><strong>HRR20</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4a</td>
<td>0.784 (0.696 - 0.882)</td>
<td>5.5×10^{-5}</td>
</tr>
<tr>
<td>Model 4b</td>
<td>0.801 (0.709 - 0.905)</td>
<td>3.8×10^{-4}</td>
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<tr>
<td><strong>HRR30</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4a</td>
<td>0.779 (0.688 - 0.882)</td>
<td>8.5×10^{-5}</td>
</tr>
<tr>
<td>Model 4b</td>
<td>0.793 (0.697 - 0.902)</td>
<td>4.0×10^{-4}</td>
</tr>
<tr>
<td><strong>HRR40</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4a</td>
<td>0.807 (0.709 - 0.918)</td>
<td>1.2×10^{-3}</td>
</tr>
<tr>
<td>Model 4b</td>
<td>0.821 (0.718 - 0.938)</td>
<td>3.7×10^{-3}</td>
</tr>
<tr>
<td><strong>HRR50</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4a</td>
<td>0.801 (0.702 - 0.915)</td>
<td>1.1×10^{-3}</td>
</tr>
<tr>
<td>Model 4b</td>
<td>0.810 (0.707 - 0.929)</td>
<td>2.6×10^{-3}</td>
</tr>
</tbody>
</table>

Relative risks for all-cause and CAD (Coronary artery disease) mortality were estimated using a Cox proportional hazard model. Hazard ratio and CI (Confidence Interval) are shown per standard deviation increase in HRR (Heart rate recovery). Two sensitivity analysis were performed in which two adaptations of model 4 were ran:
Model 4: age, sex, BMI (Body Mass Index), exercise capacity, exercise duration, systolic blood pressure, hyperlipidaemia, use of diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, ever received a doctor diagnosis of cancer, lung disease, or diabetes mellitus, smoking behaviour, physical activity behaviour, a family history of CVD (Cardiovascular Disease), the Townsend deprivation index and resting heart rate;
Model 4a: covariates of model 4, to which the maximum heart rate was added;
Model 4b: covariates of model 4a, to which the blood count (erythrocytes and leucocytes) was added.
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