ORIGINAL RESEARCH

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 disease[1,3,5,6] and others in symptomatic patients who were referred for an exercise test.[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.[8] Despite this knowledge, HRR is commonly determined at 1 minute after termination of exercise.[1,3,6] Recently, a study by McCrory et al[9] 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

From the Departments of Cardiology (Y.J.v.d.V., P.v.d.H., N.V.) and Genetics (P.v.d.H.), University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; Durrer Center for Cardiogenetic Research, Netherlands Heart Institute, Utrecht, the Netherlands (P.v.d.H.).

An accompanying Table S1 is available at http://jaha.ahajournals.org/content/7/8/e008341/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Niek Verweij, MSc, Department of Cardiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9700RB Groningen, the Netherlands. E-mail: n.verweij@umcg.nl

Received December 12, 2017; accepted March 1, 2018.

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.

authors to other researchers for purposes of reproducing the results or replicating the procedure upon reasonable request.

Individuals were selected from the UK Biobank resource. The UK Biobank is a large population-based study that recruited up to 502 713 individuals aged 40 to 69 years from the general population between 2006 and 2010. The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee and all participants provided written informed consent to participate in the UK Biobank study. Detailed methods used by UK Biobank have been described elsewhere.[10]

In total, 79 217 participants underwent an exercise ECG test during the baseline visit that was made available for download by the UK Biobank. Of those, 66 271 exercise ECGs contained beat-to-beat information of the RR interval and others contained an error related to the ECG device ("Error reading file C:\DOCUME~1\UKBBUser\LOCALS~1\ Temp \ONL10.tmp"). Before exercise, the participant's risk category was calculated based on: (1) cardiovascular risk factors including chest pain during physical activity, chest pain at rest, the inability to walk/cycle, high weight, high blood pressure, or a heart condition; (2) missing information on weight, blood pressure, or length; and (3) other factors including pregnancy and having a pacemaker. Participants eligible for this study (N=49 497) did not have any of these cardiovascular risk factors at the time of the cardiovascular test assessment and were placed in category 1. Individuals in category 1 were allowed to cycle at 50% of their maximum workload, which was calculated according to age, height, weight, resting heart rate, and sex. Participants not included in the current study were placed in category 2 (n=7654, 30% workload: low risk), category 3 (n=1990, 0% workload: medium risk), or category 4 (n=7130, pretest only: high risk). During the cardiovascular test, participants were equipped with 4 ECG electrodes placed on the right and left antecubital fossa and wrist that recorded a 3-lead ECG at 500 HZ during pretest (15 seconds), activity (6 minutes), and recovery (1 minute) of exercise. The full exercise test protocol can be found elsewhere.[11]

Although participants in category 1 were not found to have any cardiovascular risk factors referred to in the exercise ECG protocol from the UK Biobank at the time of the cardiovascular assessment, we assessed their medical history obtained through hospital records and included only individuals without a history of cardiovascular disease based on *International Statistical Classification of Diseases and Related Health Problems* (*ICD*) codes I00-I78 as well as operation codes and self-reported history of cardiovascular disease, including cerebrovascular accident; angina; cardiac surgery; percutaneous coronary intervention; heart failure (including cardiomyopathy); pericarditis, myocarditis, or endocarditis; arrhythmias; bundle branch block; valvular disease; pericardial effusion; rheumatic heart disease; and coronary and noncardiac artery disease (eg, aneurisms), as previously described.[12]

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[13] followed by detection of individual QRS peaks by the Construe algorithm.[14] 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.[15] Abnormal RR interval values of RR <0286 or RR >2 seconds, corresponding to a heart rate slower than 30 beats per minute or faster than 210 beats per minute, were discarded.[15] Further data cleaning of abnormal RR intervals was performed according to Chen and Liu's method[16] for automatic detection of outliers in time series by interpolation, incorporated in the "tsclean" 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±3, 20±3, 30±3, 40±3, and 50±3 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.

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[17] 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.[18] 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 lipidemias 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.[19] 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,[3,9] but 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[3] 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,[9] 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,[20] 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.

Table 1. Baseline Characteristics

	Sample	All-Cause Mortality	CAD Mortality
No.	40 727	536	39
Age, y	56.1±8.1	61.2±6.6	60.4±5.9
Sex (male)	44.6	56.3	79.0
BMI, kg/m^2	26.8±4.3	27.1±4.2	28.3±4.7
Exercise capacity, W	88.0±22.8	84.5±22.4	93.4±19.2
Exercise duration, s	428.0±32.4	421.3±52.1	427.4±23.9
Systolic blood pressure, mm Hg	129.9±15.8	135.1±15.8	139.2±13.8
Diabetes mellitus, %	3.8	7.1	12.0
Hyperlipidemia, %	12.9	19.6	23.0
Smoking behavior, %			
Ideal	57.5	42.0	51.0
Intermediate	33.5	41.8	28.0
Poor	9.0	16.2	21.0
Physical activity behavior, %			
Ideal	71.3	67.2	67.0
Intermediate	23.3	25.0	18.0
Poor	5.4	7.8	15.0
Family history of CVD, %	39.3	42.4	49.0
CVD, %	0	0	0
Pulmonary disease, %	12.4	14.4	10.0
Malign cancer, %	9.2	26.1	5
Benign cancer, %	7.2	9.1	15
β-Blockers, %	1.5	2.4	-
Calcium channel blockers, %	4.0	6.0	5.0
ACEIs, %	5.2	8.0	10.0
Diuretics, %	4.1	7.5	8.0
Townsend deprivation index	−0.003±0.979	0.035±0.937	0.191±1.001
Resting heart rate, beats per min	71.3±11.2	73.4±12.7	73.8±15.0
Maximum heart rate, beats per min	119.0±13.5	118.2±13.0	116.4±14.3
Hemoglobin concentration, g/dL	14.3±1.2	14.4±1.3	15.0±1.2
White blood cell count, $\times 10^{11}$ cells/L	7.0±1.9	7.4±2.5	7.4±2.2
Heart rate recovery at 10 to 50 s			
HRR10, beats per min	18.4±7.7	15.6±7.6	13.0±5.6
HRR20, beats per min	24.2±8.9	20.8±9.1	18.8±7.3
HRR30, beats per min	28.6±9.6	24.7±9.6	22.6±9.2
HRR40, beats per min	31.9±10.1	28.0±10.1	25.4±9.1
HRR50, beats per min	34.3±10.4	30.2±10.4	27.7±9.7

Continuous variables are presented as mean±SD and binary variables as percentages. ACEIs indicates angiotensin-converting enzyme inhibitors; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; HRR, heart rate recovery.

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

Table 2. Associations of HRR With All-Cause and CAD Mortality

	All-Cause Mortality		CAD Mortality	
	HR (CI)	*P* Value	HR (CI)	*P* Value
HRR10				
Model 1	0.651 (0.591–0.718)	5.1×10^{-18}	0.398 (0.264–0.598)	9.6×10^{-06}
Model 2	0.758 (0.684–0.839)	1.1×10^{-07}	0.505 (0.328–0.777)	1.9×10^{-03}
Model 3	0.783 (0.707–0.867)	2.7×10^{-06}	0.540 (0.351–0.831)	5.1×10^{-03}
Model 4	0.827 (0.742–0.921)	5.8×10^{-04}	0.524 (0.329–0.833)	6.3×10^{-03}
HRR20				
Model 1	0.643 (0.585–0.707)	6.0×10^{-20}	0.481 (0.332–0.696)	1.1×10^{-04}
Model 2	0.769 (0.695–0.852)	4.5×10^{-07}	0.637 (0.428–0.949)	2.7×10^{-02}
Model 3	0.802 (0.724–0.888)	2.1×10^{-05}	0.684 (0.459–1.019)	6.2×10^{-02}
Model 4	0.848 (0.760–0.946)	3.1×10^{-03}	0.680 (0.440–1.051)	8.2×10^{-02}
HRR30				
Model 1	0.635 (0.577–0.698)	6.0×10^{-21}	0.478 (0.330–0.691)	8.7×10^{-05}
Model 2	0.773 (0.697–0.857)	1.1×10^{-06}	0.646 (0.432–0.966)	3.3×10^{-02}
Model 3	0.809 (0.729–0.897)	6.0×10^{-05}	0.697 (0.466–1.043)	7.9×10^{-02}
Model 4	0.857 (0.766–0.959)	7.3×10^{-03}	0.691 (0.444–1.076)	1.0×10^{-01}
HRR40				
Model 1	0.643 (0.585–0.707)	6.0×10^{-20}	0.466 (0.323–0.674)	4.8×10^{-05}
Model 2	0.799 (0.720–0.887)	2.5×10^{-05}	0.640 (0.426–0.961)	3.1×10^{-02}
Model 3	0.836 (0.753–0.927)	7.2×10^{-04}	0.690 (0.460–1.037)	7.4×10^{-02}
Model 4	0.894 (0.798–1.001)	5.2×10^{-02}	0.680 (0.435–1.065)	9.2×10^{-02}
HRR50				
Model 1	0.644 (0.586–0.708)	8.0×10^{-20}	0.475 (0.330–0.685)	6.7×10^{-05}
Model 2	0.809 (0.729–0.899)	7.3×10^{-05}	0.664 (0.443–0.996)	4.8×10^{-02}
Model 3	0.844 (0.761–0.937)	1.4×10^{-03}	0.714 (0.476–1.072)	1.0×10^{-01}
Model 4	0.898 (0.802–1.007)	6.5×10^{-02}	0.707 (0.452–1.105)	1.3×10^{-01}

Hazard ratios for all-cause and coronary artery disease (CAD) mortality were estimated using a Cox proportional hazard model. Hazard ratio (HR) and confidence interval (CI) are shown per SD increase in heart rate recovery (HRR). Four regression models were used to study the association between HRR and mortality. Model 1: univariate. Model 2: age, sex, body mass index (BMI), and exercise capacity. Model 3: age, sex, BMI, exercise capacity, exercise duration, systolic blood pressure (SBP), diabetes mellitus, hyperlipidemia, smoking behavior, current physical activity behavior, and a family history of cardiovascular disease (CVD). Model 4: age; sex; BMI; exercise capacity; exercise duration; SBP; hyperlipidemia; use of diuretics, β-blockers, calcium channel blockers, or angiotensin-converting enzyme inhibitors; ever received a doctor diagnosis of cancer, lung disease, or diabetes mellitus; smoking behavior; physical activity behavior; a family history of CVD; Townsend deprivation index; and resting heart rate.

factors as well as for risk factors for mortality in general and cardiovascular medicine use (model 4), only HRR10, HRR20, and HRR30 remained predictive of all-cause mortality. Table 2 shows a time trend in HRs for the multivariate models, with HRs increasing for every 10-second increase in HRR. HRR10 was the most significant risk predictor and conferred the lowest HR. In general, *P* values and HRs increased incrementally with every 10-second increase of HRR in all multivariable models.

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 [$P=1.1\times10^{-07}$]) and CAD (HR, 0.506; CI,

0.328–0.779 [$P=2.0\times10^{-03}$]) 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, $P<1.0\times10^{-18}$). 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

This research was conducted using the UK Biobank. We would like to thank the Center for Information Technology of the University of Groningen for their support and for providing access to the Peregrine high-performance computing cluster. We thank Ruben N. Eppinga, MD; Tom Hendriks, MD; M. Yldau van der Ende, BSc; M. Abdullah Said, BSc; the University of Groningen; the University Medical Center Groningen, Department of Cardiology; and Yanick Hagemeijer, MSc, for their contributions to the extraction and processing of data in the UK Biobank. None of the mentioned contributors received compensation, except for their employment at the University Medical Center Groningen. We also thank Dr Thomas Teijeiro for his assistance with the Construe algorithm.

Sources of Funding

Verweij is funded by a Marie Sklodowska-Curie Global Fellowship (call: H2020-MSCA-IF-2014, project ID: 661395) and a "Nederlandse Organisatie voor Wetenschappelijk Onderzoek" VENI grant (016.186.125) in support of research into ECG changes in response to exercise.

Disclosures

None.

References

1. Morshedi-Meibodi A, Larson MG, Levy D, O'Donnell CJ, Vasan RS. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (the Framingham Heart Study). *Am J Cardiol*. 2002;90:848–852.
2. Lipinski MJ, Vetrovec GW, Froelicher VF. Importance of the first two minutes of heart rate recovery after exercise treadmill testing in predicting mortality and the presence of coronary artery disease in men. *Am J Cardiol*. 2004;93:445–449.
3. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med*. 2005;352:1951–1958.
4. Myers J, Tan SY, Abella J, Aleti V, Froelicher VF. Comparison of the chronotropic response to exercise and heart rate recovery in predicting cardiovascular mortality. *Eur J Cardiovasc Prev Rehabil*. 2007;14:215–221.
5. Jouven X, Escolano S, Celermajer D, Empana JP, Bingham A, Hermine O, Desnos M, Perier MC, Marijon E, Ducimetiere P. Heart rate and risk of cancer death in healthy men. *PLoS One*. 2011;6:e21310.
6. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med*. 2000;132:552–555.
7. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med*. 1999;341:1351–1357.
8. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, Takeda H, Inoue M, Kamada T. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *J Am Coll Cardiol*. 1994;24:1529–1535.
9. McCrory C, Berkman LF, Nolan H, O'Leary N, Foley M, Kenny RA. Speed of heart rate recovery in response to orthostatic challenge. *Circ Res*. 2016;119:666–675.
10. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779.
11. UK biobank cardio assessment version 1.0. April 2011. Available at: http://biobank.ctsu.ox.ac.uk/crystal/docs/Cardio.pdf. Accessed September 23, 2017.
12. Verweij N, Eppinga RN, Hagemeijer Y, van der Harst P. Identification of 15 novel risk loci for coronary artery disease and genetic risk of recurrent events, atrial fibrillation and heart failure. *Sci Rep*. 2017;7:2761.
13. WFDB-software package. Available at: https://physionet.org/physiotools/wfdb.shtml. Updated 2016. Accessed October 3, 2016.
14. Teijeiro T, Felix P, Presedo J, Castro D. Heartbeat classification using abstract features from the abductive interpretation of the ECG. *IEEE J Biomed Health Inform*. 2018;22:409–420.
15. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996;93:1043–1065.
16. Chen C, Liu LM. Joint estimation of model parameters and outlier effects in time series. *J Am Stat Assoc*. 1993;88:284–297.
17. Townsend P, Phillimore P, Beattie A. *Health and Deprivation: Inequality and the North*. London, England: Routledge; 1988.
18. Tyrrell J, Wood AR, Ames RM, Yaghootkar H, Beaumont RN, Jones SE, Tuke MA, Ruth KS, Freathy RM, Davey Smith G, Joost S, Guessous I, Murray A, Strachan DP, Kutalik Z, Weedon MN, Frayling TM. Gene-obesogenic environment interactions in the UK biobank study. *Int J Epidemiol*. 2017;46:559–575.
19. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD; American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586–613.
20. Lantz B. The large sample size fallacy. *Scand J Caring Sci*. 2013;27:487–492.
21. Lauer MS, Okin PM, Larson MG, Evans JC, Levy D. Impaired heart rate response to graded exercise. Prognostic implications of chronotropic incompetence in the Framingham Heart Study. *Circulation*. 1996;93:1520–1526.
22. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation*. 1992;85:I77–I91.
23. Coote JH. Recovery of heart rate following intense dynamic exercise. *Exp Physiol*. 2010;95:431–440.
24. Alger K. Wearable technology is revolutionizing fitness. Available at: http://raconteur.net/technology/wearables-are-the-perfect-fit. Updated 2014. Accessed August 13, 2017.
25. Lamkin P. Wearable tech market to be worth $34 billion by 2020. Available at: https://www.forbes.com/sites/paullamkin/2016/02/17/wearable-tech-market-to-be-worth-34-billion-by-2020/#5f4e78c83cb5. Updated 2016. Accessed August 13, 2017.
26. Dooley EE, Golaszewski NM, Bartholomew JB. Estimating accuracy at exercise intensities: a comparative study of self-monitoring heart rate and physical activity wearable devices. *JMIR Mhealth Uhealth*. 2017;5:e34.
27. El-Amrawy F, Nounou MI. Are currently available wearable devices for activity tracking and heart rate monitoring accurate, precise, and medically beneficial? *Healthc Inform Res*. 2015;21:315–320.

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).

	All-cause mortality		**CAD mortality**	
	Hazard ratio (CI)	p-value	Hazard ratio (CI)	p-value
HRR10				
Model 4a	0.782 (0.698 - 0.875)	2.0×10^{-05}	0.506 (0.315 - 0.815)	5.0×10^{-03}
Model 4b	0.801 (0.713 - 0.900)	2.0×10^{-04}	0.506 (0.315 - 0.813)	4.9×10^{-03}
HRR20				
Model 4a	0.784 (0.696 - 0.882)	5.5×10^{-05}	0.657 (0.413 - 1.045)	7.6×10^{-02}
Model 4b	0.801 (0.709 - 0.905)	3.8×10^{-04}	0.660 (0.415 - 1.049)	7.9×10^{-02}
HRR30				
Model 4a	0.779 (0.688 - 0.882)	8.5×10^{-05}	0.660 (0.407 - 1.069)	9.1×10^{-02}
Model 4b	0.793 (0.697 - 0.902)	4.0×10^{-04}	0.665 (0.410 - 1.079)	9.9×10^{-02}
HRR40				
Model 4a	0.807 (0.709 - 0.918)	1.2×10^{-03}	0.637 (0.387 - 1.050)	7.7×10^{-02}
Model 4b	0.821 (0.718 - 0.938)	3.7×10^{-03}	0.644 (0.390 - 1.065)	8.6×10^{-02}
HRR50				
Model 4a	0.801 (0.702 - 0.915)	1.1×10^{-03}	0.660 (0.396 - 1.098)	1.1×10^{-01}
Model 4b	0.810 (0.707 - 0.929)	2.6×10^{-03}	0.669 (0.401 - 1.118)	1.2×10^{-01}

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.

Heart Rate Recovery 10 Seconds After Cessation of Exercise Predicts Death

Yordi J. van de Vegte, Pim van der Harst and Niek Verweij

J Am Heart Assoc. 2018;7:e008341; originally published April 5, 2018;
doi: 10.1161/JAHA.117.008341
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980