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Protective Role of Resting Heart Rate on All-Cause and Cardiovascular Disease Mortality

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Abstract

Objective—To study the protective role of lower resting heart rate (RHR) on cardiovascular disease (CVD) and all-cause mortality.

Patients and Methods—Participants (n=51,936) who received a baseline medical examination between January 1, 1974 and December 31, 2002 were recruited from the Cooper Clinic, Dallas, Texas. They completed a medical questionnaire and underwent clinical evaluation. Participants with CVD or cancer, those who did not achieve at least 85% of their age-predicted maximal heart rate or who had <1 year of mortality follow-up were excluded from the study. SAS was used for statistical analysis. Relative risks and 95% confidence intervals of all-cause and CVD mortality across RHR categories were estimated using Cox proportional hazard models.

Results—Highest cardiorespiratory fitness (CRF) with lower mortality was found in individuals with a RHR <60 bpm. Similarly, participants with a higher RHR, >80 bpm, were at greater risk for both CVD and all-cause mortality when compared with RHR <60 bpm. This analysis was followed by the stratification of the data by hypertension, where hypertensive individuals with high RHRs (≥80 bpm) were found at greater risk for CVD and all-cause mortality when compared to those with hypertension and lower RHRs (<60 bpm). Additionally unfit individuals with high RHR had the greatest risk for CVD and all-cause mortality. Interestingly, the unfit with low RHR group had a similar risk for both CVD and all-cause mortality as the fit with high RHR group.

Conclusion—Lower levels of CRF and higher RHR are linked with greater CVD and all-cause mortality[1].

[1]**List of Abbreviations:** BP= Blood pressure, CHD= Coronary heart disease, CRF= Cardiorespiratory Fitness, CV= Cardiovascular, CVD = CV Disease, HTN= Hypertension, PA= Physical Activity, RHR= Resting heart rate.

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INTRODUCTION

Heart rate is an important factor that is widely used in determining the health of an individual, especially overall cardiovascular (CV) health (1). Tachycardia is a well-known predictor of CV disease (CVD) and related morbidity and mortality, both with and without other CV risk factors, such as hypertension (HTN) (2). Two decades of epidemiological data have suggested a significant association between higher CVD morbidity and mortality and increasing resting heart rate (RHR) (3, 4) (5, 6). RHR has been established as a parameter of great prognostic value, with high RHR serving as an indicator of increased CVD and all-cause mortality after controlling for platelet counts, hemoglobin concentration, white blood counts, total protein and other associated factors (7). In patients with coronary heart disease (CHD), high RHR serves as an indicator of total and CVD mortality, irrespective of other major CHD risks factors (3). High RHR has also been linked to higher deaths and CVD complications in patients with type II diabetes (8). Several benefits are associated with lower RHR, which can potentially be achieved by regular physical activity (PA), which acts via the autonomic nervous system, with an increased relationship between vagal/sympathetic tone (9).

Cardiorespiratory fitness (CRF) is a well-studied marker to assess the risk of CVD and to determine CV health in adults, adolescents and children (10–12). Daily PA which can increase CRF, results in significant positive effects on musculoskeletal and CV systems, as well as beneficial effects on metabolic, physiological, endocrine and immune mechanisms and function (13). Lack of PA causes approximately 250,000 deaths per year in the United States (14), whereas regular PA decreases the risk of CVD, delays the onset of high blood pressure (BP) and reduces BP in patients with HTN. In addition lower CRF is associated with higher RHR (15). Most large epidemiological studies do not have objective measures of PA, but we have reported that a maximal treadmill exercise test can be a good indicator of habitual PA and is a strong predictor of mortality (16).

In the present study, we assessed the relationship between RHR and CVD and all-cause mortality in fit and unfit patients with and without HTN in a large cohort from the Aerobics Center Longitudinal Study (ACLS).

METHODS

Participants

Participants were recruited from the patients of Cooper Clinic, Dallas, Texas, who received a baseline medical examination between January 1, 1974 and December 31, 2002. The clinic serves anyone who elects to come for an examination and patients come from all 50 states. Among 57,242 participants aged ≥ 20 years at baseline, we excluded individuals with CVD or cancer (n=2,785) and those who had <1 year of follow-up for mortality (n=1,135). These exclusion criteria were used to minimize potential bias due to underlying subclinical conditions that might affect mortality. The final analysis for the current study included 53,322 men and women. The ACLS was reviewed and approved annually by the institutional review board at the Cooper Institute. Participants read and signed an approved informed consent form prior to the baseline and follow-up medical examinations.

Instruments and Procedures

Medical Examination—Participants completed a medical history questionnaire consisting of demographic questions, lifestyle habits (e.g. smoking, drinking, PA), and past and present chronic disease history (e.g. hypertension, diabetes, hypercholesterolemia). Participants also underwent a clinical evaluation including a treadmill maximum exercise test, body

composition assessment, blood chemistry analysis, blood pressure measurement, and a physical examination by a physician.

Self-Reported Medical Information—As part of the medical questionnaire, participants self-reported the following: smoking status (current smoker or non-current smoker); alcohol use (heavy drinker if >14 drinks/week were consumed for males or >7 drinks/week were consumed for females); and PA (sedentary classification if no leisure-time physical activity in the 3 months prior to the medical examination). High BP was defined as measured systolic BP ≥ 140 mm Hg, or diastolic BP ≥90 mm Hg. Participants also self-reported whether they were currently diagnosed with HTN or diabetes or had a personal or parental history of CVD (myocardial infarction or stroke) and cancer.

Clinical Evaluation—Participants' clinical evaluations were completed after a 12-h fast and have been described in detail elsewhere (17, 18). Briefly, height and weight were measured in light clothing and without shoes using a standard clinical scale and stadiometer. Body mass index (BMI) was calculated as kg/m^2. Resting BPs were measured using mercury manometers following the American Heart Association protocol (19), and measurement began after at least 5 min of seated rest. Two or more readings separated by 2 min were averaged. If the first two readings differed by more than 5 mm Hg, additional readings were obtained and averaged. RHR was measured with the participants recumbent after 5-min rest and was obtained from the ECG. Fasting serum samples were analyzed for lipids and glucose using automated bioassays and in accordance with the Centers for Disease Control and Prevention Lipid Standardization Program. CRF was quantified by the total time of a maximal symptom-limited treadmill test using a modified Balke protocol (20). Participants were encouraged to reach their maximum effort and the test was terminated once the participant requested to stop because of exhaustion or when the physician stopped the test due to medical reasons. Classification of CRF was determined based on quintiles of treadmill time for males and females in each age group (20–39, 40–49, 50–59, and ≥60 yrs) from the entire ACLS population, with the lowest 20% classified as "unfit" based on our earlier studies (21, 22).

Mortality surveillance

For mortality surveillance, participants were followed from the baseline examination through the date of death for decedents or December 31, 2003 for survivors. The National Death Index was the primary data source for mortality surveillance, augmented with death certificates. The underlying cause of death was determined from the National Death Index report or by a nosologist's review of official death certificates obtained from the department of vital records in the decedent's state of death. CVD mortality was defined as International Classification of Diseases, Ninth Revision (ICD-9) codes 390 to 449.9 before 1999 and ICD-Tenth Revision (ICD-10) codes I00 to I78 during 1999 to 2003.

Statistical analysis

SAS software (version 9.12; SAS Institute, Cary, NC) was used for statistical analysis. Significance was set at $P < 0.05$ for all statistical analyses. Participants were divided into 4 RHR categories: 1) <60 bpm, 2) 60–69 bpm, 3), 70–79 bpm, and 4) >80 bpm based on earlier studies (23). Baseline characteristics were determined for all participants and across RHR categories.

We used Cox proportional hazard models to estimate the relative risks and 95% confidence intervals of all-cause and CVD mortality across RHR categories. Hazard models were additionally developed using a stratified analysis for self-reported HTN to minimize the potential confounding effect of HTN medications in individuals with physician diagnosed

HTN, because some medications affect resting BP levels. All models were adjusted for the following potential confounders: age, sex, examination year, BMI, smoking status, heavy alcohol drinking, PA, parental CVD, abnormal resting or exercise electrocardiogram, diabetes, BP, self-reported HTN, hypercholesterolemia, and CRF. Finally, we conducted joint stratification analyses by RHR and CRF status. When we used interaction terms in the multivariable Cox regression, we found no significant interactions between RHR and CRF on all-cause (p=0.95) and CVD mortality (p=0.64) risks.

Results

A total of 53,322 men and women were observed in this study, with a mean follow-up of 15.0 ± 8.5 years and a total of 3,125 deaths. Table 1 shows baseline characteristics for the overall study population and each RHR category. Individuals with a RHR <60 bpm had the highest CRF, the lowest percentage of physical inactivity, and the lowest prevalence of HTN, diabetes, and hypercholesterolemia compared to the higher RHR categories.

Table 2 shows the hazard ratios for all-cause and CVD mortality for the 4 RHR categories. There was a significant positive linear trend for both all-cause and CVD mortality across incremental levels of RHR. Individuals with a higher RHR had a greater risk for all-cause mortality and CVD mortality (table 2).

We additionally examined the hazard ratios for all-cause and CVD mortality by RHR stratified by self-reported HTN (Table 3). There were suggestions of positive linear trends across RHR categories for both all-cause and CVD mortality, but the trends were statistically significant only for all-cause mortality in those without self-reported HTN (p=0.02) and for CVD mortality for those with self-reported HTN (p=0.04). Individuals with HTN and high RHRs (≥80 bpm) were at a 1.38 times greater risk for all-cause mortality compared to those with HTN and lower RHRs (<60 bpm). Likewise, hypertensive individuals with high RHRs had a 1.52 times greater risk for CVD mortality compared to hypertensives with low RHR.

Table 4 shows hazard ratios for all-cause mortality and CVD mortality by combined RHR and CRF categories. Two combined RHR categories (low [<80 bpm] and high [≥ 80 bpm]) and 2 CRF classifications (fit and unfit) were used for these analyses. The fit and low RHR group was used as a reference for both all-cause and CVD mortality. Unfit individuals with high RHR had the greatest risk, 2.21, for all-cause mortality. Interestingly, the unfit and low RHR group had a similar risk for all-cause mortality as the fit and high RHR (1.48 and 1.50, respectively). Similar results were seen with CVD mortality. The unfit, high RHR group had a 2.34 times greater risk for CVD mortality compared to the fit and low RHR group. The fit and high RHR group was at 1.73 times higher risk and the unfit and low RHR at 1.48 times higher risk for CVD mortality, compared to the fit and low RHR group.

DISCUSSION

Previous epidemiological studies have shown a relationship between RHR and mortality (24–26). Low RHR has been linked to greater survival rate and lower susceptibility to chronic diseases. This study focused on establishing a link between RHR and all-cause and CVD mortality in fit and unfit individuals with and without systemic HTN. Our results were consistent with several other studies, including the Chicago Epidemiologic Study (27), the Framingham Study (25) and the study conducted by Sharper et al in middle-aged British men (28, 29). Our study included middle-aged men and women and dealt with many potential confounders related to RHR and CVD, including PA and CRF, which are often lacking in other studies. Greater PA has been linked to higher CRF (30–32), which is

correlated with lower RHR and lower mortality and reduced risk of many chronic diseases, including CVD. In our study, two different models for calculating the hazard ratios for all-cause and CVD mortality were used to evaluate associations between RHR and all-cause and CVD mortality. By these models, RHR ≥80 is a risk factor for CVD, while RHR <60 is associated with significantly lower mortality. We have further stratified the data by self-reported HTN, which has potential to be associated with reduced RHR, especially for those taking beta-adrenergic blocking agents and non-dihydropyridine calcium entry blocking agents. Without self-reported HTN significant differences were noted between the mortality rate with low and high RHR in all-cause mortality and with self-reported HTN in CVD mortality.

Our study also analyzed the relationship between RHR and CRF, by stratifying participants based on their CRF levels, determined by a maximal treadmill exercise test. These analyses clearly indicate a higher risk for both CVD and all-cause mortality with greater RHR (>80) and lower level of fitness. Also, fit individuals with both low and high RHR have lower CVD and all-cause mortality as compared to unfit individuals. Fit subjects with low RHR have the lowest mortality risk. These data further strengthen our hypothesis that low RHR and greater CRF significantly decrease all-cause and CVD mortality, although high CRF did not completely eliminate the negative effect of high RHR on mortality risk.

Several prior studies have shown the prognostic value of low RHR for lower overall morbidity and mortality. Hsia et al (27) showed that higher RHR was associated with greater risk of CHD events in cohort of post-menopausal women, particularly in younger individuals (33). Another study by Jouven et al demonstrated that, in 23 years of follow up in the Paris Prospective Study in middle aged men free of any known CVD, higher RHR is a confirmed risk factor for sudden cardiac death (24). The Chicago Epidemiological Study has shown that higher RHR was associated with higher CVD and non-CVD mortality, and was an independent risk factor for sudden cardiac death (27). The Framingham Study also provided evidence for the same finding with a greater association of higher RHR with CVD in men as compared to women (25). They have also found an independent association between higher non-CVD deaths with higher RHR. Similar results were obtained in the study on middle aged British men by Sharper et al. (24).

Our study, although similar to previous reports, provided a more comprehensive analysis by including both men and women and an assessment of CRF. The association between greater PA and CRF, lower RHR and lower all-cause and CVD mortality can be explained by several physiological mechanisms (35). Moderate PA has been considered extremely beneficial for the CV health, via improvements in immune function and several metabolic adaptations, leading to improvements in CVD and CHD risk factors, such as HTN, obesity, diabetes, hypercholesterolemia and inflammation (36). Any amount of PA above the baseline level leads to increases in blood flow, which increases the vasodilatory capacity of the arteries and further improves vascular tone and anti-atherosclerotic activity, leading to reduced inflammation and reduced risk for coronary artery disease (37). Other studies have demonstrated an increased production of nitric oxide NO (37) and heat shock proteins (HSP) (38), leading to increased breakdown of reactive oxygen species (ROS) and reducing oxidative damage. All these mechanisms are related to CRF and hence could lead to a reduction in RHR, which may lead to reduced all-cause and CVD mortality. Our study is also indicative of the protective role of lower RHR on all-cause and CVD mortality irrespective of the CRF level. Although the exact mechanism for the association of lower RHR with reduced mortality remains uncertain, it could be argued that lower RHR leads to reduced shear stress on the endothelial walls, decreases adverse ventricular remodeling and prevents imbalance of myocardial oxygen supply and demand, all of which could prevent major CVD events and other disease outcomes, leading to decreased mortality (39).

Additionally, the lower RHR is indicative of favorable influence on the autonomic nervous system, tilting the balance toward augmented vagal tone as opposed to sympathetic tone, thus having a favorable impact on the CV system and risk of major CVD events and mortality (40). In this regard, Rovera et al. also showed that in post-myocardial infarction patients, CVD mortality decreases whenever the autonomic status changes toward increased vagal activity irrespective of exercise training (40). Improvements in vagal tone have also been linked with reduced arrhythmias in chronic heart failure patients (41).

This study has several strengths and weaknesses. The strength includes large sample size including both men and women, and the long follow-up period of 15.1±8.5 years. Limitations include self-reported baseline chronic conditions, PA measurement, history of HTN, diabetes, and CVD. Due to the widespread geographic distribution of patients evaluated at the Cooper Clinic, we were unable to verify all reported chronic conditions. However, based on a random sample of verified events, it appears that an acceptable level of agreement exists between the participant's self-reported history and their medical records (the percentage of agreement between self-reported events and participant medical records was 88%, 89%, 98% and 92% for myocardial infarction, stroke, HTN, and diabetes) (17, 42, 43). The current study was conducted in a population of non-Hispanic white individuals from mid- to high socio-economic status and primarily college graduates. Although this study included most of the major potential confounding factors affecting RHR, however a detailed medication history was not available, which might have affected the RHR of the studied population. However, we found consistent results regardless of HTN status, since beta blocking agents used to treat this may affect RHR levels. Also, it is possible that the baseline RHR might have changed over the long follow-up duration, which might have influenced the study findings. There was also no follow- up of the confounders, such as smoking, alcohol drinking, which could have affected the observed associations between RHR and all-cause and CVD mortality. Finally, we do not have data on markers of social/ personal autonomy and heart rate variability, which could be addressed in future studies.

Conclusion

A low level of RHR was associated with a lower risk of dying from all-cause and from CVD. A similar pattern of associations was observed in participants with and without self-reported physician-diagnosed HTN. Those unfit and with higher RHR had the highest risk of all-cause and CVD mortality. Also, lower RHR was protective irrespective of the CRF levels. All of these data indicate that lower RHR is related to lower all-cause and CVD mortality and higher levels of CRF may further enhance this association.

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Table 1

Baseline characteristics of 53,322 men and women according to resting heart rate.

	Baseline Resting Heart Rate (beats per minute, bpm)				
	All	**<60**	**60–69**	**70–79**	**≥80**
	n = 53,322	**n = 23,805**	**n = 17,866**	**n = 8,727**	**n = 2,924**
Age (y)	43.97 ± 9.90	43.81 ± 9.92	44.17 ± 9.87	43.95 ± 9.82	44.20 ± 10.12
Females (%)	24.48	18.33	27.67	31.31	34.75
Resting heart rate (bpm)	61.48 ± 10.77	52 ± 5	64 ± 3	73 ± 3	86 ± 7
Body-mass index (kg/m^2)	25.50 ± 3.73	25.08 ± 3.34	25.68 ± 3.79	26.04 ± 4.19	26.26 ± 4.47
Cardiorespiratory fitness (Maximum METs)	11.13 ± 2.54	12.12 ± 2.57	10.65 ± 2.21	9.98 ± 2.11	9.36 ± 2.07
Unfit (%)*	15.04	7.26	16.64	25.98	36.05
Resting systolic blood pressure (mmHg)	119 ± 14	118 ± 14	120 ± 14	122 ± 14	125 ± 16
Resting diastolic blood pressure (mmHg)	80 ± 10	78 ± 9	80 ± 10	82 ± 10	84 ± 11
High blood pressure (%)†	21.01	15.40	22.43	27.91	37.41
Self-reported hypertension (%)	14.28	11.50	14.88	17.66	23.26
Fasting glucose (mmol/l)	5.47± 0.92	5.39 ± 0.71	5.47 ± 0.87	5.59 ± 1.13	5.82 ± 1.64
Diabetes (%)‡	5.20	3.78	5.47	6.93	9.88
Total cholesterol (mmol/l)	5.33 ± 1.03	5.22 ± 0.98	5.38 ± 1.02	5.45 ± 1.07	5.54 ± 1.15
Hypercholesterolemia (%)§	26.61	23.34	27.84	30.53	34.03
Current smoker (%)	16.43	15.32	17.27	17.85	16.11
Heavy alcohol drinking (%)‖	17.71	17.70	17.82	17.83	16.79
Physically Inactive (%)¶	70.77	20.00	33.38	40.47	45.49
Parental cardiovascular disease (%)	26.84	26.15	26.76	28.18	29.04
Abnormal resting or exercising Electrocardiogram (%)	7.40	7.02	7.49	7.57	9.40

Continuous variables are reported as mean ± SD and categorical variables are reported as percentage.

*Defined as the lower 20% in each age- and sex-specific distribution of maximal treadmill exercise test duration from the entire Aerobics Center Longitudinal Study population.

†Defined as systolic or diastolic blood pressure ≥140/90 mm Hg.

‡Defined as fasting glucose ≥7 mmol/l, current therapy with insulin, or physician diagnosis.

§Defined as total cholesterol ≥6.21 mmol/l or physician diagnosis.

|| Defined as alcohol drinks >14 per week for men >7 per week for women.

¶ Defined as no leisure-time physical activity in the 3 months before the examination.

Table 2

Hazard Ratios of All-Cause and Cardiovascular Disease Mortality by Resting Heart Rate.

Resting Heart Rate (beats per minute)	n	All-Cause Mortality			Cardiovascular Disease Mortality		
		Deaths	Hazard Ratio (95% CI)		Deaths	Hazard Ratio (95% CI)	
			Model 1*	Model 2†		Model 1*	Model 2†
<60	23,805	1,194	1.00 (Reference)	1.00 (Reference)	378	1.00 (Reference)	1.00 (Reference)
60–69	17,866	1013	1.01 (0.93–1.11)	0.93 (0.86–1.02)	356	1.06 (0.92–1.23)	0.96 (0.83–1.12)
70–79	8,727	610	1.11 (1.00–1.23)	0.99 (0.90–1.10)	220	1.15 (0.97–1.37)	1.03 (0.86–1.22)
≥ 80	2,924	308	1.66 (1.45–1.89)	1.38 (1.21–1.58)	127	1.87 (1.52–2.30)	1.51 (1.22–1.87)
P for linear trend			< 0.0001	0.002		< 0.0001	0.005

*Adjusted for age, sex, examination year, body mass index, smoking status, heavy alcohol drinking, physical activity, parental cardiovascular disease, abnormal electrocardiogram, diabetes, high blood pressure, self-reported hypertension, and hypercholesterolemia.

†Adjusted for model 1 plus maximal METs.

Table 3

Hazard Ratios of All-Cause and Cardiovascular Disease Mortality by Resting Heart Rate in Stratified Analysis by Self-Reported Hypertension

Resting Heart Rate (beats per minute)	All-Cause Mortality		Cardiovascular Disease Mortality	
	Self-Reported Hypertension Hazard Ratio (95% CI)*		Self-Reported Hypertension Hazard Ratio (95% CI)*	
	No	Yes	No	Yes
<60	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
60–69	0.91 (0.82–1.01)	0.98 (0.83–1.16)	0.96 (0.80–1.15)	0.95 (0.74–1.22)
70–79	1.01 (0.89–1.14)	0.96 (0.79–1.16)	1.03 (0.83–1.28)	1.02 (0.77–1.35)
≥ 80	1.38 (1.16–1.62)	1.38 (1.10–1.72)	1.45 (1.09–1.95)	1.52 (1.10–2.09)
P for linear trend	0.02	0.06	0.08	0.04

*Adjusted for age, sex, examination year, body mass index, smoking status, heavy alcohol drinking, physical activity, parental cardiovascular disease, abnormal electrocardiogram, diabetes, high blood pressure, hypercholesterolemia, and maximal METs.

Table 4

Hazard Ratios of All-Cause and Cardiovascular Disease Mortality by Combined Categories of Resting Heart Rate and Cardiorespiratory Fitness

Resting Heart Rate (beats per minute)	All-Cause Mortality		Cardiovascular Disease Mortality	
	Cardiorespiratory Fitness Hazard Ratio (95% CI)*		Cardiorespiratory Fitness Hazard Ratio (95% CI)*	
	Fit	Unfit	Fit	Unfit
Low (<80)	1.00 (Reference)	1.48 (1.35–1.63)	1.00 (Reference)	1.48 (1.27–1.73)
High (≥80)	1.50 (1.25–1.79)	2.21 (1.88–2.60)	1.73 (1.30–2.31)	2.34 (1.81–3.01)

*Adjusted for age, sex, examination year, body mass index, smoking status, heavy alcohol drinking, physical activity, parental cardiovascular disease, abnormal electrocardiogram, diabetes, high blood pressure, self-reported hypertension, hypercholesterolemia, and maximal METs.