Relation of Resting Heart Rate to Risk for All-Cause Mortality by Gender After considering Exercise Capacity (the Henry Ford Exercise Testing Project)

Amer I. Aladin, MD[a], Seamus P. Whelton, MD, MPH[a], Mouaz H. Al-Mallah, MD, MPH[b,c], Michael J. Blaha, MD, MPH[a], Steven J. Keteyian, PhD[b], Stephen P. Juraschek, MD, PhD[a], Jonathan Rubin, MD[a], Clinton A. Brawner, PhD[b], and Erin D. Michos, MD, MHS[a,*]

Whether resting heart rate (RHR) predicts mortality independent of fitness is not well established, particularly among women. We analyzed data from 56,634 subjects (49% women) without known coronary artery disease or atrial fibrillation who underwent a clinically indicated exercise stress test. Baseline RHR was divided into 5 groups with <60 beats/min as reference. The Social Security Death Index was used to ascertain vital status. Cox hazard models were performed to determine the association of RHR with all-cause mortality, major adverse cardiovascular events, myocardial infarction, or revascularization after sequential adjustment for demographics, cardiovascular disease risk factors, medications, and fitness (metabolic equivalents). The mean age was 53 ± 12 years and mean RHR was 73 ± 12 beats/min. More than half of the participants were referred for chest pain; 81% completed an adequate stress test and mean metabolic equivalents achieved was 9.2 ± 3. There were 6,255 deaths over 11.0-year mean follow-up. There was an increased risk of all-cause mortality with increasing RHR (p trend <0.001). Compared with the lowest RHR group, participants with an RHR ≥90 beats/min had a significantly increased risk of mortality even after adjustment for fitness (hazard ratio 1.22, 95% confidence interval 1.10 to 1.35). This relationship remained significant for men, but not significant for women after adjustment for fitness (p interaction <0.001). No significant associations were seen for men or women with major adverse cardiovascular events, myocardial infarction, or revascularization after accounting for fitness. In conclusion, after adjustment for fitness, elevated RHR was an independent risk factor for all-cause mortality in men but not women, suggesting gender differences in the utility of RHR for risk stratification. **(Am J Cardiol 2014;114:1701−1706)**

Elevated resting heart rate (RHR) is associated with an increased risk of cardiovascular disease (CVD) and mortality.[1−13] Additionally, subjects with an elevated RHR are generally less fit as assessed by peak oxygen uptake.[14] Exercise capacity, as estimated in metabolic equivalents (METS), has also been shown to be inversely associated with mortality.[15,16] Two recent studies from the Copenhagen Male Study[6] and the Veterans Affair system[2] suggested that RHR may be an important risk predictor of mortality independently of fitness; however, whether gender might influence this relationship is unknown. RHR is known to be higher in women,[17] and for a given age, women have lower peak oxygen uptake and predicted METS.[18,19] Gender-related differences regarding pathophysiology, manifestation, and prognosis of CVD have been reported.[20] Therefore, gender may modify the relation of RHR with mortality and CVD. Using the Henry Ford ExercIse Testing Project (The FIT Project), we sought to assess if there are gender differences in the association of RHR with mortality and major adverse cardiac events (MACE) after adjusting for clinical characteristics and estimated exercise capacity.

Methods

The FIT Project[21] is a retrospective cohort study investigating the implications of physical fitness and/or exercise capacity on CVD outcomes and mortality. Patients were excluded from the registry if they were <18 years old at the time of stress testing or if they were evaluated by pharmacologic stress testing. The FIT Project is comprised of the following: (1) directly measured exercise data (exercise duration, METS); (2) retrospective collection of medical history and medication treatment data taken at the time of the stress test; (3) retrospective verification and supplementation of supporting clinical data using the electronic medical record (EMR) and administrative databases; and (4) epidemiologic follow-up for total mortality and select nonfatal outcomes by the way of linkage with the death

[a]Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins School of Medicine, Baltimore, Maryland; [b]Division of Cardiovascular Medicine, Henry Ford Health System, Detroit, Michigan; and [c]King Abdulaziz Cardiac Center, Riyadh, Kingdom of Saudi Arabia. Manuscript received May 27, 2014; revised manuscript received and accepted August 26, 2014.

The authors Aladin and Whelton contributed jointly toward this work.

Funding source: None.

See page 1706 for disclosure information.

*Corresponding author: Tel: (+410) 502 6813; fax: (+410) 502 0231.
E-mail address: edonnell@jhmi.edu (E.D. Michos).

0002-9149/14/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2014.08.042

Table 1
Participant characteristics by resting heart rate groups

Baseline Heart Rate Groups	1	2	3	4	5	p-value for trend
Heart rate (beats/minutes)*	54.6 (35-59)	64.8 (60-69)	74.2 (70-79)	83.8 (80-89)	96.6 (90-121)	<0.001
Age (years)†	55.0 (13.3)	54.2 (12.4)	52.9 (12.3)	52.3 (12.1)	51.7 (12.4)	<0.001
Female	36.5%	45.6%	50.7%	54.2%	57.0%	<0.001
White	62.2%	64.2%	64.8%	63.4%	62.4%	<0.001
Black	30.9%	28.3%	27.8%	29.7%	30.7%	<0.001
Other	6.9%	7.4%	7.3%	6.9%	6.8%	0.235
Smoker	44.2%	42.6%	40.4%	40.5%	40.5%	<0.001
Family history of coronary artery disease	50.3%	51.2%	51.9%	52.4%	51.5%	0.064
Diabetes Mellitus	14.6%	15.1%	17.3%	21.8%	25.3%	<0.001
Dyslipidemia	43.0%	42.8%	43.1%	43.9%	41.7%	0.109
Anti- Hypertension med use	47.4%	42.2%	40.0%	41.8%	45.9%	<0.001
Atrioventricular-blocker use‡	36.9%	28.2%	23.5%	21.1%	22.4%	<0.001
Lipid lowering medicine	21.6%	20.0%	19.2%	20.3%	19.0%	<0.001
Atherosclerotic Cardiovascular Disease Risk Score†	13.8	12.2	11.3	11.6	12.1	<0.001
Systolic blood pressure (mm Hg)†	129.3 (19)	129.7 (19)	130.7 (18)	132.4 (19)	134.9 (19)	<0.001
Diastolic blood pressure (mm Hg)†	79.5 (10)	80.3 (10)	81.3 (10)	82.0 (10)	83.3 (10)	<0.001
Low density lipoprotein (mg/dL)†	124.9 (36)	126.5 (36)	127.0 (37)	127.4 (38)	127.5 (39)	0.001
High density lipoprotein (mg/dL)†	51.3 (16)	51.4 (16)	51.3 (16)	50.7 (15)	50.3 (16)	<0.001
Triglycerides§ (mg/dL)	117 (82,171)	123 (86,181)	127 (87,186)	132 (92,197)	139 (94,206)	<0.001
Metabolic Equivalents achieved†	10.0 (3)	9.6 (3)	9.2 (3)	8.7 (3)	8.0 (3)	<0.001
Adequate study¶	62.8%	76.3%	84.1%	88.3%	90.6%	<0.001

* Mean and minimum-maximum values.
† presented as mean and standard deviation, unless otherwise indicated.
‡ AV -nodal blocker use was classified as beta-blockers, calcium channel blockers, amiodarone, and/or digitalis.
§ Median and Inter-quartile range.
¶ An adequate study was defined as achieving ≥85% age-predicted maximal heart rate.

registry and medical claims files. FIT project was approved by the Institutional Review Board committee at Henry Ford Hospital.

We analyzed data from 69,885 consecutive patients who underwent physician-referred treadmill stress testing from 1991 to 2009 at Henry Ford Hospital in Detroit, Michigan, which is part of a large, vertically integrated (both health care insurer and health care provider) health system. Patients without a recorded RHR (n = 570), with known coronary artery disease ([CAD]; n = 10,106), previous congestive heart failure (n = 864), previous atrial fibrillation or flutter (n = 1,160), or those referred for arrhythmia (n = 551) were excluded from this study. Known CAD was defined as previous myocardial infarction (MI), percutaneous coronary intervention, coronary artery bypass surgery, or previous documented obstructive CAD on an angiogram. Previous congestive heart failure was defined as a clinical diagnosis of heart failure with reduced ejection fraction or with preserved ejection fraction at baseline. Previous atrial fibrillation was defined as a clinical diagnosis of at least paroxysmal atrial fibrillation at baseline. Those with missing data on METS (n = 774) were excluded from analyses that adjusted for exercise capacity. This left a total of 56,634 patients available for overall analyses and 55,860 for analyses adjusted for METS.

All patients underwent routine clinical treadmill stress testing using the standard Bruce protocol. Treadmill stress tests completed using a protocol other than the standard Bruce protocol were not eligible for this study. The treadmill test was symptom-limited and was terminated if the patient had exercise-limiting chest pain, shortness of breath, or other limiting symptoms as assessed by the supervising clinician independent of the achieved heart rate. In addition, testing could be terminated early at the discretion of the supervising clinician for significant arrhythmias, abnormal hemodynamic responses, diagnostic ST-segment changes, or if the participant was unwilling or unable to continue.

RHR and blood pressure (BP) were taken in the seated position before stress testing by a trained clinical personnel. Target heart rate (HR) was calculated as 85% of the age-predicted maximal HR determined by the formula: 220 − age. An "adequate" test was defined as achieving ≥85% age-predicted maximal HR. Exercise capacity, expressed in estimated METS, was calculated by the Quinton treadmill controller based on achieved speed and elevation. Maximum METS achieved was recorded from the total treadmill time and was categorized into 4 groups (<6, 6 to 9, 10 to 11, ≥12). Other potential stress test information including perfusion imaging or echocardiographic results and HR recovery were not available in this data set.

A medical history data including age, gender, race (self-report), indication for stress test, anthropomorphic data, risk factor burden, past medical history, and active medication use was obtained by a nurses and/or exercise physiologists immediately before the stress test. Indication for stress test referral was provided by the referring physician and subsequently categorized into common indications (e.g., chest pain, shortness of breath, pre-operative evaluation, and so forth). Risk factors were defined and gathered prospectively by self-report and then augmented by a retrospective search of the EMR. Smoking status was defined as listed per EMR; current smoking was defined as self-reported active smoking at the