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Park, JI
Shin, SY
Park, SK
et al.

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Usefulness of the Integrated Scoring Model of Treadmill Tests to Predict Myocardial Ischemia and Silent Myocardial Ischemia in Community-Dwelling Adults (From the Rancho Bernardo Study)

Running title: Predicting myocardial ischemia with integrated scoring model of treadmill tests

Joong-Il Park, MD[a,b], So-Young Shin MD[a,d], Sue K Park,[a,c], Elizabeth Barrett-Connor, MD[a *]

[a]Epidemiology Division, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA

[b]Division of Cardiology, Department of Medicine, Veterans Health Service Medical Center, Seoul, Korea

[c]Department of Biomedical Science, Department of Preventive Medicine, and Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

[d]Global Medical Affairs Women's HealthCare, Bayer HealthCare Pharmaceuticals, Seoul, Korea

Correspondence:

Elizabeth Barrett-Connor, MD,

Distinguished Professor,

Epidemiology Division, Department of Family Medicine and Public Health

School of Medicine, University of California, San Diego

9500 Gilman Drive

La Jolla, CA 92093-0607, USA

Tel: 1.858.534.3720; Fax: 1.858.246.0298; Email: ebarrettconnor@ucsd.edu

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Abstract

To investigate the association between analyses of sub-maximal treadmill exercise test (TMT) and long-term myocardial ischemia (Mis) and silent Mis in community-dwelling older adults, 898 Rancho Bernardo Study participants (mean age 55) without coronary heart disease underwent TMT and were followed up to 27 years. The main outcome measures are incidence of Mis and silent Mis. During follow up, 97 Mis and 103 silent Mis events occurred. We measured ST change, inability to achieve target heart rate (iTHR), abnormal heart rate recovery (HRR), and chronotropic incompetence (ChI). Each parameter was a significant predictor for Mis and silent Mis. An integrated scoring model was based on these 4 parameters and defined as sum of numbers of abnormal parameters. After multiple adjustments, an integrated scoring model independently predicted Mis and silent Mis. The incidence rates of abnormalities of parameters are 36.5% for 1 abnormality, 9.1% for 2 abnormalities, and 2.0% for 3 or 4 abnormalities. Compared to those with normal results, participants with 1 or 2 abnormalities had significantly increased risk for Mis (HR 1.79 or 2.34) and silent Mis (HR 1.80 or 2.64), respectively. Participants with 3 or more positive findings showed an even higher risk for Mis (HR 7.96, [3.02-21.00]) and silent Mis (HR 3.22, [0.76-13.60]). In conclusion, ST change, ChI, abnormal HRR, iTHR, and integrated scoring model of TMT were independent predictors of long-term Mis and silent Mis in an asymptomatic middle-aged population. Management of ChI or abnormal HRR in an asymptomatic population may prevent future ischemic heart disease and thus improve the quality of life.

Key Words: Chronotropic incompetence; Heart Rate Recovery; Myocardial ischemia; ST change; Target Heart Rate; Treadmill Exercise Test

Introduction

It is well known that chronotropic incompetence (ChI) and abnormal heart rate recovery (HRR) are independent predictors of major adverse cardiovascular events and overall mortality (**1-4**). However, the independent value of the treadmill exercise test (TMT) used as a screening tool in asymptomatic adults to predict future coronary artery disease, and especially to predict silent ischemia, is not yet known (**5, 6**). The present study was designed to assess ST change, ChI, inability to achieve target heart rate (iTHR), abnormal HRR, and integrated analysis of these parameters as predictors of myocardial ischemia (Mis) and silent Mis in community-dwelling asymptomatic older adults followed up to 27 years.

Methods

The Rancho Bernardo Study is a prospective population-based study of older adults residing in a suburban southern California community. The cohort of residents enrolled was quite homogeneous—they were almost entirely Caucasian and most were white-collar workers. Between 1972 and 1974, a total of 1789 community-dwelling adults participated in a heart disease risk factor survey, which served as the baseline visit for the present study. Participants with a history of CHD (myocardial infarction, angina, or coronary artery bypass surgery) were excluded from the TMT. The data of 898 participants who underwent TMT at baseline are used for this analysis (Figure 1). The study protocol was approved by the Human Research Protection Program at the University of California, San Diego; all participants gave written informed consent prior to participation. Participants were followed by annual mailed questionnaires, and they returned for research clinic visits approximately every four years through 1999, up to 27 years.

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A sub-maximal TMT was administered to participants (**7, 8**); exclusions included aortic stenosis, congestive heart failure, severe hypertension, R-on-T type premature ventricular contractions, ventricular tachycardia, parasystolic focus, atrial flutter, congenital heart disease, second reschedule required others. The exercise test was terminated for any of the following reasons; 1) subjective response: the subject was unwilling or unable to continue exercise; 2) development of potential hazards to the subject; 3) attainment of near-maximal exercise--exercise was stopped if the subject attained age-predicted target heart rate (THR) and maintained it for one minute, if the subject maintained THR until the end of the ongoing exercise stage, or if subject's heart rate exceeded target heart rate by 8 beats/min, whichever occurred first (**8, 9**). A test was considered to be positive if 1) ST depression or elevation of 1 mm or more was recorded by the visual coders, 2) the ST integral fell by at least 10 diV-sec from its resting value to a value of 10 gV-sec or less, or 3) the ST integral rose by at least 10 gV-sec from its resting value.

Three non-electrocardiographic measures were defined as: 1) an abnormal HRR–a decrease of <22 bpm after 2 min of recovery(**10**); 2) ChI--the inability to achieve 80% of heart rate reserve, using a standard equation to define the percentage heart rate reserve [(maximal heart rate - resting heart rate)/ (174-0.54 x age) - (resting heart rate) x 100] (**11**); 3) THR was considered achieved when 90% of maximal heart rate predicted for subject's age was attained(**2**).

The primary outcomes were Mis and silent Mis. Myocardial ischemia, determined by using standard epidemiologic methods (such as annual mailed questionnaires and interviews at regular clinic visits), consisted of a history of myocardial infarction, angina pectoris, coronary revascularization, or coronary artery bypass graft history.

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Silent Mis was defined as ≥1 ischemic resting ECG abnormalities, newly revealed at a follow-up visit with no history of myocardial infarction, angina pectoris, or chest pain not meeting the Rose algorithm.

i) “ECG coronary probable”--major Q or QS wave [Minnesota Code 1.1, 1.2]; complete left bundle branch block [Minnesota Code 7.1.1]

ii) “ECG coronary possible”--small Q or QS wave [Minnesota Code 1.3]; ST depression [Minnesota Code 4.1 – 4.3]; T wave items [Minnesota Code 5.1 – 5.3] (**12**).

No Evidence of Cardiovascular Disease was defined as: no ECG changes and no history of myocardial infarction, angina pectoris, or chest pain (≥ 30 min). Data on vital status was collected on all participants. More than 99% of this cohort was followed for vital status by annual mailer through 1999.

Death certificates were obtained for all decedents and coded for cause of death by a certified nosologist using the 9th revision of the "International Classification of Diseases, Adapted" (ICDA-9). Deaths due to coronary heart disease included coronary death, myocardial infarction, coronary insufficiency, and angina (ICD-9 codes 410.00-414.00). We classified deaths due to coronary heart disease as apparent myocardial ischemia.

Categorical variables are reported as numbers (percentages), and continuous variables are presented as means (standard deviation). Cox proportional hazards regression analyses were performed to obtain multivariate-adjusted hazard ratios of Mis and silent Mis of those who had abnormal test results during the TMT versus those with normal test results. Hazard ratios were adjusted for age by decade, sex, cholesterol level, history of diabetes, and smoking. We performed the supremum test for proportional hazards assumption with 1000 replications in Cox regression model.

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Although TMT had a marginal significance in the test of proportionality, we used the time-dependent Cox regression model because the other exposure variables fit the proportionality assumption. We restricted study subjects who had performed TMT in our analyses, and there were no missing in exposure variables such as TMT and target HR. There was 1 missing in the variables of HRR and ChI. Also our main exposure variables such as ST change, THR, HRR, ChI were binomial scales (achievement vs. no-achievement; positive vs. negative etc.), not continuous scales, and so there were no outliers. There was no interaction effect between the main exposure variable and the other confounders in our multivariate models. A two-tailed $p<0.05$ was considered statistically significant. Data were analyzed using the SAS statistical package (SAS institute, Chicago, Illinois).

Results

The baseline characteristics of participants are provided in Table 1; 898 Rancho Bernardo Study participants underwent TMT and were followed for up to 27 years (mean age at baseline 55.04±14.85, 481 were women); 218 (24.3%) were current smokers, 366 (40.8%) were daily drinkers, 180 (20.0%) had metabolic syndrome, and 38 (4.2%) had diabetes mellitus.

Fifty-three (5.9%) participants showed positive TMT (ST change). Overall, 418 participants (46.5%) were unable to achieve their THR. 22 participants (2.5%) had abnormal HRR, and chronotropic incompetence (ChI) was detected in 56 participants (6.2%). In Cox proportional hazards models, after adjusting for age, sex, cholesterol level, diabetes, and smoking history, positive TMT was independently associated with Mis (HR 1.72, 95% CI 0.83-3.59) and silent Mis (HR 2.16, 95% CI

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1.16-4.19); iTHR was associated with Mis (adjusted HR 2.11, 95% CI 1.25-3.57) and silent Mis (HR 2.16, 95% CI 1.33-3.50) regardless of causes for stopping TMT (Table 2, Figure 2 and 3). Abnormal HRR was also independently associated with Mis (adjusted HR 5.30, 95% CI 2.14-13.15) and silent Mis (HR 1.29, 95% CI 1.18-9.37). And ChI was associated with Mis (HR 1.92, 95% CI 1.01-3.65) but not silent Mis (adjusted HR 0.99, 95% CI 0.40-2.47) (Table 2, Figures 2 and 3).

Even in the sub-analysis excluding ST segment abnormalities, iTHR was persistently associated with higher Mis (adjusted HR 2.10, 95% CI 1.22-3.61) and silent Mis (adjusted HR 1.74, 95% CI 1.05-2.90), and abnormal HRR remained a predictor of Mis (adjusted HR 3.94, 95% CI 1.34-11.63) (Table 3).

The number of positive findings among these 4 measures (positive TMT, iTHR, abnormal HRR, and ChI) was closely associated with higher Mis and silent Mis. The incidence rates of abnormalities of parameters are 36.5% for 1 abnormality, 9.1% for 2 abnormalities, and 2.0% for 3 or 4 abnormalities. Compared with normal findings, any one abnormal finding predicted a 1.79-fold higher risk for Mis and 1.80-fold higher risk for silent Mis. Two and three or more positive findings were associated with a 2.34- and 7.96-fold higher risk for Mis and 2.64- and 3.22-fold higher risk for silent Mis, respectively (Table 4).

Discussion

Silent Mis is defined as objective documentation of Mis in the absence of angina or angina equivalents. Its clinical significance is now well established, but there are few prognostic studies of silent ischemia in the general population or in truly asymptomatic populations (**13-15**). Silent Mis is usually diagnosed when there is asymptomatic ST depression during TMT or ambulatory ECG monitoring; however,

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whether ChI, iTHR, or abnormal HRR can predict future silent Mis in a community-dwelling population had not been evaluated.

Chronotropic incompetence (ChI), broadly defined as the inability of the heart to increase its rate commensurate with increased activity or demand, is common in patients with cardiovascular disease, produces exercise intolerance that impairs quality of life, and is predictive of increased mortality and coronary heart disease risk, independent of various confounding factors, including age, gender, physical fitness, traditional cardiovascular risk factors, and ST change during exercise (**2, 16, 17**). Our study showed that ChI was associated with Mis (HR 1.92, 95% CI 1.01-3.65) but not silent Mis (adjusted HR 0.99, 95% CI 0.40-2.47)

Traditionally, the ability to reach THR was used as a signal of sufficient cardiac loading during the TMT; iTHR is also considered an impaired chronotropic response. In this cohort study, iTHR was associated with 2.11- and 2.16-fold increased risk for Mis and silent Mis, respectively. And it was persistently associated with risk for Mis and silent Mis in only GXT-negative subjects.

Abnormal HRR after exertion also has been associated with increased all-cause mortality risk in a variety of asymptomatic and diseased populations (**18**), even after adjusting for severity of cardiovascular disease, left ventricle (LV) function, and exercise capacity (**19**). In alignment with earlier reports, our study confirmed that abnormal HRR was a strong predictor of future Mis including silent Mis (Table 3).

ChI, iTHR, and abnormal HRR have a similar pathophysiologic mechanism, failure of heart rate control. The mechanisms that have been proposed to explain ChI and iTHR are 1) underlying autonomic nervous system imbalance; 2) reduced myocardial viability; and 3) attenuated protective response to permit greater myocardial perfusion in the presence of narrowed coronary arteries (**20**). The ability

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of HRR following exercise is related to the capacity of the cardiovascular system to reverse autonomic nervous system and baroreceptor adaptations that occur during exercise, often termed vagal (**21, 22**). We investigated whether integration of these parameters can show an additive value of prediction for future ischemic heart disease including silent Mis.

Strengths of this study include the well-characterized, population-based TMT of community-dwelling older adults, and the long-term follow up. There are also limitations. First, Mis and silent Mis were not confirmed by coronary angiogram or imaging studies, which may raise questions on validity of our data. Second, these results may not be applied to the general population because the cohort of residents was quite homogeneous--almost entirely Caucasian. Third, TMT protocol is submaximal, which would make it difficult to assess the prognostic importance of exercise capacity.

Our study demonstrates that an integrated analysis was useful to predict Mis and silent Mis in the Rancho Bernardo cohort. The higher number of abnormal findings was well correlated with increased risk for Mis and silent Mis. Participants with three or more abnormal findings had more than a 7-fold increased risk for Mis compared to those without abnormal findings, which clearly shows that these parameters provide further information to predict future Mis and silent Mis.

To our knowledge, this is the first paper to show the predictive value of integrated analysis of sub-maximal TMT for Mis and, to a lesser degree, silent Mis, in healthy, community-dwelling older adults followed for up to 27 years.

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Figures

Figure 1. Summary of study population (CHD—coronary heart disease; Mis—myocardial ischemia).

Figure 2. Myocardial ischemia event free survival probability per *(A)* ST change, *(B)* inability to achieve target heart rate, *(C)* abnormal heart rate recovery, and *(D)* chronotropic incompetence.

Figure 3. Silent myocardial ischemia event free survival probability per *(A)* ST change, *(B)* inability to achieve target heart rate, *(C)* abnormal heart rate recovery, and *(D)* chronotropic incompetence.

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