

Abnormal heart rate recovery after exercise predicts coronary artery disease severity

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Abstract

Background: *Slow heart rate recovery (HRR) after exercise is considered to represent impaired parasympathetic tone and to be a predictor of all-cause and cardiovascular mortality, but the independent value of abnormal HRR in predicting the presence and severity of coronary artery disease (CAD) is unknown. The aim of this study was to evaluate these relationships in our patients.*

Methods: *This prospective cross-sectional study included 208 patients (67.3% men), aged 34 to 74 (mean 53) years. Patients who had an ischemic response during symptom-limited exercise testing underwent selective coronary angiography. The value for HRR was defined as the decrease in heart rate from peak exercise to one minute after the exercise ceased. Eighteen beats per minute was defined as the lowest normal value for HRR.*

Results: *Significant CAD was detected in 140 (67.3%) patients. There were 66 (31.7%) patients with an abnormal HRR. In multivariable logistic regression analysis adjusted for established CAD risk factors, abnormal HRR was independently correlated with the extent of major epicardial coronary involvement ($p = 0.04$). The sensitivity, specificity, positive and negative predictive values, and accuracy of abnormal HRR for predicting extensive CAD were 48%, 83.3%, 72.7%, and 63.4%, respectively. There was also a significant correlation between HRR one minute after exercise and smoking ($p = 0.004$), chronotropic variables ($p = 0.001$), and the calculated risk score for the exercise test ($p = 0.03$). There was no significant correlation between HRR and other risk factors including age and gender, left ventricular systolic function, and history of myocardial infarction.*

Conclusions: *There is a significant correlation between abnormal post-exercise HRR at one minute and the extent of major epicardial coronary involvement. (Cardiol J 2011; 18, 1: 47–54)*

Key words: **treadmill testing, heart rate recovery, coronary artery disease, myocardial ischemia**

Introduction

The prognostic value of slow heart rate recovery (HRR) after exercise in predicting cardiovascular disease and mortality has been established [1–4]. Initial increases in heart rate (HR) with exercise are due to parasympathetic withdrawal, while sympa-

thetic activation is responsible for HRs greater than 100 beats/minute. In the first minutes following cessation of exercise, the rapid decrease in HR is principally determined by parasympathetic reactivation [5]. Although slow HRR is associated with less autonomic nervous system responsiveness, the underlying mechanisms linking slow HRR to in-

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creased cardiovascular morbidity are not well understood. It is possible that slow HRR is associated with a higher susceptibility for atherosclerosis. Previous studies of patients referred for cardiac angiography for suspected coronary artery disease (CAD) suggest an association between slow HRR and higher atherosclerotic burden [4]. Furthermore, slow HRR has been observed to be associated with several risk factors for atherosclerosis [6].

The aim of this study was to evaluate HRR after treadmill exercise testing (TET) as a predictor of the presence and severity of atherosclerotic coronary artery involvement, by focusing on the correlation between HRR and various parameters related to CAD (demographics, risk factors, chronotropic variables, and calculated risk score for the exercise test).

Methods

The cohort was derived from a prospectively obtained database of adults referred for symptom-limited treadmill testing between January 2006 and September 2008. All patients were undergoing their first TET at our institution. Patients were eligible if coronary angiography was indicated by TET results and they underwent the procedure within 90 days. Exclusion criteria included: primary cardiomyopathies; congestive heart failure NYHA classes III/IV; acute myocardial infarction within < 30 days; valvular disease; pre-excitation; congenital disease; prior abnormal coronary angiogram/intervention or surgery; known sinus node dysfunction; atrial fibrillation or other tachyarrhythmias; bradycardia; complete left bundle branch block (LBBB); pacemaker placement; use of digoxin, vasodilators, amiodarone or other antiarrhythmic drugs; fever; and those with contraindications to or an inability to perform treadmill testing or to achieve a satisfactory exercise level because of an extracardiac condition (peripheral vascular disease, sciatica, neuropathy, disability, etc). Beta-blockers and calcium channel antagonists were discontinued at least two days before the exercise test in all patients. Our Institutional Review Board approved the performance of research on this clinical database. All patients signed study consent forms and answered a questionnaire about the presence of symptoms, medication use, risk factors for CAD, and previous cardiac or noncardiac diagnoses. Hypertension was defined by a history of blood pressure > 140/90 mm Hg and/or antihypertensive drug use; diabetes mellitus and dyslipidemia (a recent total cholesterol value \geq 250 mg/dL, triglyceride \geq 150 mg/dL, HDL

< 40 mg/dL) were defined by history and/or medication use. Previous myocardial infarction was defined by pathologic Q-waves or QS complexes in the absence of QRS confounders, especially when Q-waves were present in several leads or lead groupings and accompanied by ST deviations or changes to T-waves [7].

After a 12 hour fast, and avoiding smoking or engaging in strenuous physical activity for at least three hours before the examination, TET was performed according to a symptom-limited Bruce's protocol, with continuous electrocardiographic (ECG) monitoring. Blood pressure was measured and recorded at rest, at the end of each stress stage, at peak stress, and at recovery. The test was stopped for any of the following reasons: a rating of perceived exertion > 17 (Borg scale); achievement of > 90% of age predicted maximum HR; if the subject was too fatigued to safely continue walking on the treadmill; systolic blood pressure > 250 mm Hg; typical chest discomfort; severe arrhythmias; and more than 1 mm of horizontal or downsloping ST segment depression. After peak exercise, the test was almost immediately terminated, and measurements were taken while the patients were in the sitting position. In most other studies, patients have spent at least 1–2 minutes in a 'cool-down', after achieving peak workload, and the value for the recovery of HR was defined as the reduction in the HR from the rate at peak exercise to the rate one minute after the end of exercise [3, 8]. It has been thought that the value of HRR may be affected even by the small workload during the 'cool-down', decreasing its diagnostic sensitivity [9, 10]. In addition, the implication of the workload during this period is different for each patient.

Therefore, the patients in our study did not undergo a 'cool-down'. HRR was obtained by subtracting HR at the first minute of recovery from peak HR obtained during exercise. A HRR \leq 18 beats/min was considered abnormal [10]. Maximal predicted HR was calculated as $220 - \text{age (years)}$. Chronotropic insufficiency was defined as achievement of < 80% of a patient's HR reserve (calculated as $[220 - \text{age}] - \text{resting HR}$) at peak exercise [11]. In addition, data on symptoms and estimated workload in metabolic equivalents (METs) was obtained. Functional capacity in METs was estimated using standard tables [12]. ST segments were considered abnormal if there was at least 1 mm of horizontal or down-sloping ST-segment depression 80 ms after the J point in at least three consecutive beats in two contiguous leads. Duke Treadmill Exercise Score was calculated as: $\text{exercise time} - [(5 \times \text{max}$

ST deviation) – (4 × treadmill angina index)]. Angina index was assigned a value of 0 if angina was absent, 1 if typical angina occurred during exercise, and 2 if angina was the reason the patient stopped exercising [13]. Patients were divided into low risk (LR, score ≥ 5), medium risk (MR, score between -10 and 4), and high risk (HR, score < -10) groups on the basis of the absolute calculated number.

Patients were referred for coronary angiography when indicated by TET results (ST depression more than 1 mm, or exercise-induced angina/arrhythmias), according to AHA/ACC guidelines [14]. Referring physicians were blinded to the patient's HRR and Duke Treadmill Score values (HRR values and Duke Treadmill Scores were not recorded on TET reports). Cardiologists, who were blinded to the patients' HRR and Duke Treadmill Score values, and to the hypothesis of this study, semi-quantitatively analyzed each coronary angiogram. The results were then entered into an angiographic database. Coronary artery narrowing was visually estimated and expressed as percent lumen diameter stenosis. Patients with a 50% diameter narrowing of the left main, left anterior descending, left circumflex, or right coronary arteries (or their major branches) were considered to have significant angiographic CAD. Minimal CAD was defined as diameter stenosis less than 50%. The 50% criterion was chosen to be consistent with definitions used by the Coronary Artery Bypass Graft Surgery Trialists' Collaboration [15]. Extensive or severe CAD was defined as significant stenosis of two or three major epicardial coronary arteries.

Left ventricular ejection fraction (LVEF) was semiquantitatively analyzed by contrast ventriculography or transthoracic echocardiography. Patients with a LVEF $< 50\%$ were considered to have left ventricular dysfunction.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Statistical analysis

Variables are expressed as mean \pm standard deviation and percentage. Mean differences for continuous variables between groups were examined by the independent Student t-test. Chi-square test (or Fisher exact test if applicable) was used for categorical variables. Two-tailed $p < 0.05$ was considered significant. Odds ratios (ORs) were calculated and results were presented as ORs with 95% confidence intervals (CIs). Baseline characteristics and exercise variables found to be univariate predictors were entered into multivariate models for each end

point. Multivariate logistic regression analysis was performed to determine the adjusted correlation between the significant variables and the occurrence and/or extent of CAD. SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for data storage and analysis.

Results

Of the patients who met the study criteria, 208 (142 men and 66 women) ranging in age from 34 to 74 (mean age 53 years) were included. Abnormal HRR was detected in 66 (31.7%) patients. There was no significant difference in the mean age, gender, risk factors for ischemic heart disease [except for smoking (OR 2.36, 95% CI = 1.27–4.39, $p = 0.006$)], LVEF, or history of myocardial infarction (MI) between those who had a normal or abnormal HRR (Table 1). Both groups were similar with regard to measured ST-segment depression and symptom-related reasons for test termination. Fatigue was the commonest reason for terminating the test in both groups, and the prevalence of angina or dyspnea was not statistically different (Fig. 1). Patients with a normal value of HRR had a significantly better chronotropic response during TET, compared to those who had an abnormal value. In particular, they had a lower pre-exercise resting HR (95% CI = 0.62–10.85, $p = 0.02$), higher HR reserve (95% CI = -33.7 to -10.71 , $p < 0.001$), and higher maximal HR (95% CI = -20.37 to -8.72 , $p < 0.001$) at peak exercise workload. Exercise duration (95% CI = -81.06 to 10.81 , $p = 0.13$) and functional capacity in METs (95% CI = -0.45 to 0.78 , $p = 0.4$) did not differ between the groups (Table 2).

The Duke Treadmill Score was calculated in both the normal and abnormal HRR groups. There was a significantly higher risk score in the abnormal group *vs* the normal group (95% CI = -7.34 to -3.51 , $p < 0.001$) (Fig. 2).

Major epicardial coronary artery involvement (OR = 2.93, 95% CI 1.44–5.96, $p = 0.002$) and its severity (OR = 0.21, 95% CI 0.11–0.41, $p < 0.001$) were significantly associated with abnormal HRR values at univariate analysis (Table 1, Fig. 3). Abnormal HRR was not significantly affected by which coronary artery was diseased (Fig. 4).

On multivariate logistic regression analysis, abnormal HRR was found to be independently associated with severe CAD (2/3 VD), but not with less extensive coronary involvement (minimal or 1 VD) ($p = 0.04$). The sensitivity, specificity, positive and negative predictive values, and accuracy of abnormal HRR for predicting extensive CAD

Table 1. Univariate analysis of baseline characteristics in both groups according to HRR.

Characteristics	Abnormal HRR (≤ 18 bpm)	Normal HRR (> 18 bpm)	P	Odds ratio	Confidence interval
Male gender	44 (66.7%)	96 (67.6%)	0.89	0.95	0.51–1.78
Familial CAD	8 (12.1%)	24 (16.9%)	0.37	1.47	0.62–3.48
Smoking*	20 (30.3%)	72 (50.7%)	0.006	2.36	1.27–4.39
Diabetes	20 (30.3%)	42 (29.6%)	0.91	0.96	0.51–1.82
Hypertension	34 (51.5%)	76 (53.5%)	0.78	1.08	0.60–1.94
Dyslipidemia	32 (48.5%)	58 (40.8%)	0.30	0.73	0.40–1.32
History of MI	22 (33.3%)	40 (28.2%)	0.44	0.78	0.41–1.47
LVEF < 50%	22 (33.3%)	46 (32.4%)	0.89	1.04	0.56–1.94
CAD presence*	54 (81.8%)	86 (60.6%)	0.002	2.93	1.44–5.96
Extensive CAD*	48 (72.7%)	52 (36.6%)	< 0.001	0.21	0.11–0.41
LAD involvement*	50 (75.8%)	76 (53.5%)	0.002	0.36	0.19–0.70
LCX involvement*	44 (66.7%)	48 (33.8%)	< 0.001	0.25	0.13–0.47
RCA involvement*	34 (53.1%)	44 (31.0%)	0.002	0.39	0.21–0.72

*Variables included in multivariate models for each end point; data is presented as the mean value ± SD or percentage (number) of subjects; HRR — heart rate recovery; CAD — coronary artery disease, MI — myocardial infarction; LVEF — left ventricular ejection fraction; LCX — left circumflex; RCA — right coronary artery

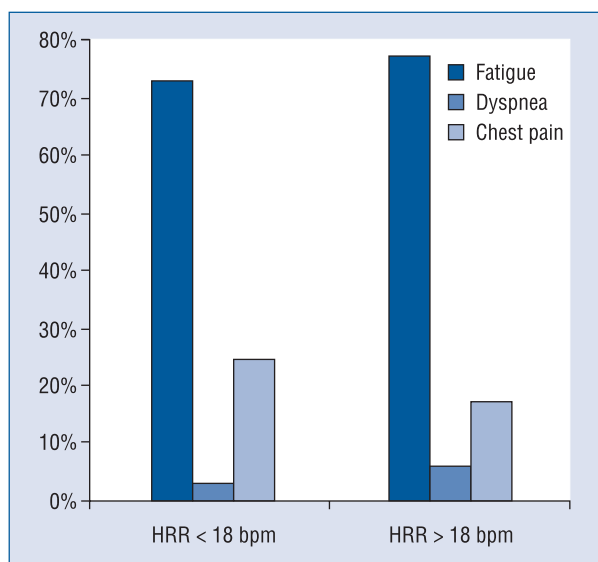


Figure 1. Reason for termination of treadmill exercise testing in both groups; HRR — heart rate recovery.

were 48%, 83.3%, 72.7%, and 63.4%, respectively. Smoking history ($p = 0.004$), higher resting and lower peak exercise HRs ($p < 0.001$), higher mean Duke Score ($p = 0.03$), and lower HR reserve ($p = 0.001$) were also significantly associated with abnormal HRR (Table 3). There was no significant correlation between HRR and other risk factors including age, gender, left ventricular systolic function, and history of MI. Patients with obstructive CAD were more likely to undergo coronary artery

bypass surgery when they had abnormal HRR. Rates of medical treatment and percutaneous coronary interventions were similar between groups (Table 4).

Discussion

Our study showed that abnormal HRR is related to the extent and severity of coronary artery involvement, the calculated risk score for the exercise test, and smoking. Patients with abnormal HRR had lower functional capacity and lower peak heart rates, and they used less of their HR reserve at peak exercise. After adjusting for confounders, abnormal HRR was independently associated with extensive CAD. These results suggest that abnormal HRR alone noted on stress ECG testing may have an independent value in predicting the extent of underlying CAD.

A significant number of reports have studied the pathophysiology of the increase in HR during TET and of its decrease at the termination of the test, events that are due to changes in tone balance between the sympathetic and the parasympathetic nervous systems [5]. The prognostic importance of the chronotropic response to exercise stress testing, and HRR after exercise, has been established [8, 10, 11]. Slow HRR has been associated with a higher incidence of all-cause mortality, sudden cardiac death (SCD), and cardiovascular events. However, the underlying mechanisms that link these relationships are not known [1]. Previous studies looking at a gen-

Table 2. Univariate analysis of age, lipid profile, and exercise performance data in both groups.

Characteristics	Abnormal HRR; mean (≤ 18 bpm)	Normal HRR; mean (> 18 bpm)	P	Confidence interval
Age (years)	53.9 \pm 10.2	52.6 \pm 9.4	0.34	-1.49 to 4.21
Triglycerides [mg/dL]	197.1 \pm 125.2	180.9 \pm 176.6	0.54	-36.36 to 68.8
HDL-cholesterol [mg/dL]	30.1 \pm 13.8	31.9 \pm 18.9	0.54	-7.72 to 4.07
LDL-cholesterol [mg/dL]	104.3 \pm 64.2	87.0 \pm 56.1	0.10	-3.48 to 38.06
Mean Duke Score*	3.2 \pm 7.7	2.2 \pm 5.8	< 0.001	-7.34 to -3.51
METs [mL/kg/min]	8.09 \pm 3.20	9.4 \pm 2.90	0.40	-0.45 to 0.78
Resting HR*	88.1 \pm 21.1	82.4 \pm 15.3	0.02	0.62 to 10.85
Exercise duration	429.7 \pm 147.7	464.9 \pm 159.7	0.13	-81.06 to 10.81
Resting SBP	127.2 \pm 15.9	128.8 \pm 20.9	0.85	-6.29 to 5.19
Resting DBP	80.1 \pm 8.4	78.9 \pm 11.6	0.44	-1.93 to 4.38
Peak SBP	157.3 \pm 20.1	160.0 \pm 24.0	0.43	-9.65 to 4.18
Peak DBP*	83.4 \pm 9.1	89.1 \pm 17.8	0.01	-10.3 to 0.94
Peak HR*	132.2 \pm 21.7	141.7 \pm 18.8	< 0.001	-20.37 to -8.72
HR reserve*	28.7 \pm 42.6	51.0 \pm 37.0	< 0.001	-33.7 to -10.71
Mean ST \downarrow [mm]	0.97 \pm 1.15	1.06 \pm 0.88	0.67	-0.53 to 0.34

*Variables included in multivariate models for each end point. Data is presented as the mean value \pm SD; HR — heart rate; SBP — systolic blood pressure; DBP — diastolic blood pressure; MET — metabolic equivalent

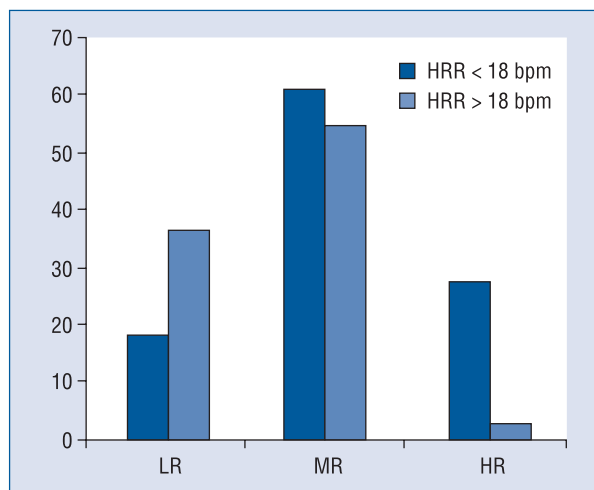


Figure 2. Prevalence of different Duke Treadmill Risk Scores in both groups; LR — low risk; MR — medium risk; HR — high risk; HRR — heart rate recovery.

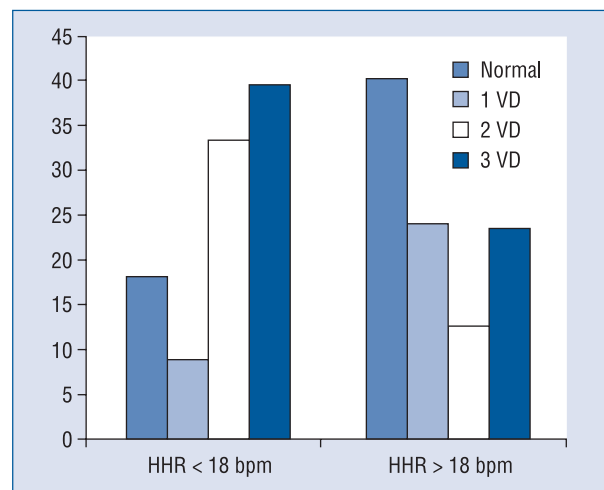


Figure 3. Relation between the number of major epicardial coronary involvements and the heart rate recovery (HRR) value.

eral cohort of patients have reported the relationship between exercise HR response and myocardial perfusion defects indicating ischemia and HRR [9, 11, 16]. Morshedi-Meibodi et al. [2], using data from the Framingham Heart Study, observed slow HRR to be associated with CAD events (defined as acute coronary syndromes or SCD), suggesting a possible relationship between slow HRR and ischemic processes. Similarly, slow HRR has been observed to be associated with several risk factors for atherosclerosis

[6]. We found a significant correlation with smoking, among CAD risk factors, and abnormal HRR. In the Lipid Research Clinic study, Gordon et al. [17] also demonstrated that HRR after TET is significantly affected by smoking status in a linear, dose-dependent manner. In their study, the decline to baseline HR after submaximal exercise was slower in smokers than in non-smokers.

Patients with a normal HRR value generally had a better performance on treadmill testing than

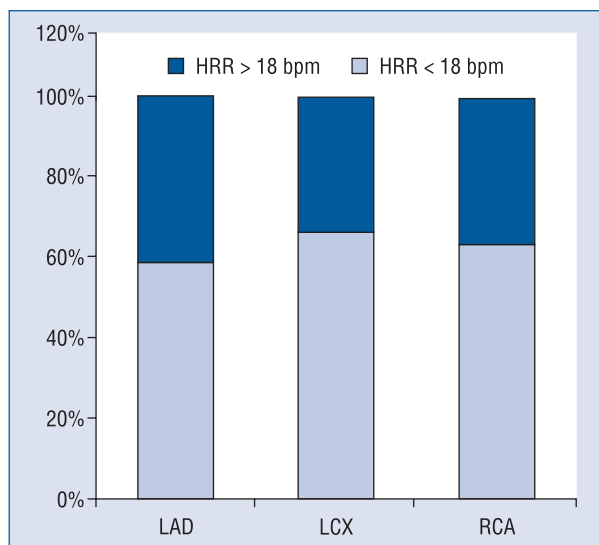


Figure 4. Major epicardial coronary involvements in both groups; LAD — left anterior descending; LCX — left circumflex; RCA — right coronary artery; HRR — heart rate recovery.

Table 3. Predictors of abnormal HRR on multivariate logistic regression analysis

Characteristics	P
CAD presence	0.23
Extensive CAD	0.04
Smoking	0.004
Mean Duck Score	0.03
Resting heart rate	< 0.001
Peak heart rate	< 0.001
Heart rate reserve	0.001

HRR — heart rate recovery; CAD — coronary artery disease

those with an abnormal value. A greater increase in the heart rate during exercise and a better chronotropic response during testing in patients with normal HRR have been reported in other studies as well [1, 3, 10].

The Duke Treadmill Score is an established exercise assessment that considers the duration of exercise, ST-segment deviation, and angina during

exercise [13]. The mean treadmill score was significantly higher in the group with abnormal HRR in our study (Table 2).

Among patients who had exercise stress testing and who had coronary angiography within 90 days, an attenuated HRR after exercise was associated with the presence of coronary artery involvement and its extent on univariate analysis, but at multivariate analysis it was independently related with only the severity of coronary artery involvement. In an older male population, Shetler et al. [18] found abnormal HRR to be predictive of increased mortality, independent of the angiographic severity of CAD. Attenuated HRR was not helpful in predicting the presence of significant angiographic coronary disease. In this study, like most of the others [3, 4, 6, 8], a two minute ‘cool-down’ after reaching peak exercise was incorporated in the test protocol. As we have said, there has been a belief that the value of HRR may be affected by the ‘cool-down’ period, decreasing its diagnostic sensitivity [9, 10]. On the contrary, Lipinski et al. [19] showed a significantly decreased HRR after the first minute of recovery in CAD patients. Like the findings in our study, HRR was not significantly affected by which coronary artery was diseased, but patients with reduced HRR had a significantly greater number of narrowed coronary arteries than those without reduced HRR. Unlike Lipinski et al. [19] and Watanabe et al. [10], who measured HRR immediately after exercise in the supine position, our measurements were done in the sitting position. HRR might be slower in the supine position because of the effect of increased venous return, which stretches the right atrial wall, and directly increases HR by stretching the sino-atrial node and/or the Bainbridge reflex by as much as 75% [20]. Accordingly, measuring HRR in the supine position shortly after termination of exercise may have a negative effect on its sensitivity for CAD detection.

Limitations of the study

Our study was limited because it involved a single tertiary-care referral center and thus was

Table 4. Treatment recommendations for patients with obstructive CAD in groups with normal and abnormal heart rate recovery (HRR).

Treatment	Abnormal HRR (≤ 18 bpm)	Normal HRR (> 18 bpm)	P
Medical follow up	7 (12.9%)	17 (19.7%)	0.36
Percutaneous coronary intervention	24 (44.4%)	47 (54.6%)	0.29
Coronary artery bypass grafting	23 (42.6%)	27 (25.6%)	0.04

open to biases of patient selection and referral patterns for coronary angiography. We tried to reduce these biases as much as possible by using standard guidelines for referring to angiography [14] and blinding the referring physicians by not recording HRR and chronotropic values in TET reports.

We did not find an association between LVEF and history of MI with abnormal HRR. This might be due to our relatively small patient population, or to the fact that only about a third of the patients in both groups had a history of MI or reduced LVEF. On the other hand, LVEF was visually and semi-quantitatively analyzed, and there may be significant inter-observer variability in its estimation.

Advancing age is strongly associated with abnormal HRR [21]. This finding may be explained by the gradual decrease in the autonomic control of HR that has been described in the aging process [21]. We found no significant correlation between age and abnormal HRR. This may be due to the relatively young age of our patients (mean age of about 54 in the abnormal HRR group).

We only used the first minute after recovery of exercise. The incorporation of more minutes might have made a difference or produced interesting results.

Conclusion and clinical implications

In conclusion, our results suggest that there is a considerable association between abnormal HRR one minute after exercise (without a "cool-down" and in the sitting position) and the severity of CAD. Moreover, the calculation of HRR value during TET could provide independent information about the extent of coronary involvement, irrespective of the traditional markers of ischemic response. In an era in which continuous effort is being put into deriving as many elements as possible from inexpensive and safe examinations, calculating HRR during TET will maximize not only the prognostic value of the study, but also the information it provides for the assessment of the extent of coronary involvement.

Our findings provide further evidence supporting the routine incorporation of HRR into TET interpretation. Future research is needed to determine how best to manage patients with abnormal heart rate recovery.

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