Heart rate recovery may predict the presence of coronary artery disease

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ABSTRACT

Objective: We investigated whether post-exercise first minute abnormal heart rate recovery (HRR1) helps to predict the presence and severity of CAD, because of some confounding data.

Methods: A cross-sectional, retrospective study was performed. Two hundred individuals were included. Gensini scores and the number of coronary artery involvements were used to evaluate the severity of CAD. Student's t-test, Mann-Whitney U test and chi-square test were used for the analysis continuous and categorical data. Spearman's correlation analysis was used to determine whether there is correlation between Gensini scoring and HRR1. Univariate and multivariate logistic regression were used to determine predictors for abnormal HRR1. ROC curve analysis was performed to detect the best sensitivity and specificity value of HRR1 in predicting CAD presence.

Results: Seventy subjects (35%) did not have CAD, and CAD was present in 130 patients (65%). HRR1 ≤21 beats with ROC analysis was determined to be the best cut off point. After adjustment between the two groups in terms of age, gender, diabetes, hypertension, dyslipidemia or smoking (all p>0.05), there was relationship CAD presence and abnormal HRR1 (OR=2.1, 95% CI: 1.1-3.9, p=0.02), but not between CAD severity and HRR1 (r=-0.13, p=0.112). The sensitivity, specificity, and the positive and negative predictive values of abnormal HRR1 ≤21 beats at first minute for predicting CAD presence were 76.1%, 41.3% (AUC=0.588, CI 95%: 0.517-0,657, p=0.039), 70.7% and 48.3%, respectively.

Conclusion: In the study abnormal HRR1 predicted the presence of CAD, but not the severity of it. *(Anadolu Kardiyol Derg 2014; 14: 351-6)*

Key words: heart rate recovery, coronary artery disease, regression analysis, diagnostic accuracy, sensitivity, specificity.

Introduction

Abnormal heart rate recovery (HRR) occurs due to insufficient vagal activity after exercise, and the prognostic value of it with regard to predicting mortality is well established (1-8). The association between HRR and coronary artery disease (CAD) angiographic severity has been investigated, and it has been reported that abnormal HRR is not predictive of the presence or severity of CAD (6, 9). However, Ghaffari et al. (10) have reported results that contradict those of previous studies, and suggest that abnormal HRR after exercise does predict the presence and severity of CAD. Moreover, Lipinski et al. (11) speculated that HRR2, which is defined as the reduction in the heart rate from the rate at peak exercise to the rate two minutes after the cessation of exercise, can predict the presence of CAD.

Because of some confounding data on the diagnostic ability of HRR related to CAD severity and presence, we investigated whether HRR at first minute (HRR1) predicted the presence and severity of CAD by measuring post-exercise HRR during a cool-down period in the sitting position after treadmill exercise testing (TET), as well as other parameters related to CAD (risk factors, ST depression, Duke score, peak heart rate, and heart rate reserve).

Methods

Study design and protocol

This was an observational retrospective study approved by the relevant Ethics Committee. We retrospectively collected data from 350 subjects that had had a coronary angiography within 30 days of exhibiting an abnormal exercise test result at our clinic. We excluded 150 subjects based on criteria described below, and collected data on 200 subjects who exhibited ST depression and reached at least 85% of the age-predicted maximal heart rate during TET, including their clinical, biochemical,

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and angiographic information. Subjects with and without CAD comprised the CAD and control groups, respectively.

Subjects

Of the subjects, 124 (62.0%) were male, 66 (33.0%) had hypertension, and 57 (28.5%) had diabetes mellitus. Fifty-two (26%) were receiving antihypertensive medication with angiotensin receptor blockers (ARB), angiotensin-converting enzyme inhibitors (ACEI), or thiazide. All subjects that reached the target heart rate were included in this study. Angiography was performed on all subjects because their exercise ECG was positive. The subjects were included if they reached 85% of their age-predicted maximal heart rate and had then undergone elective coronary angiography and ventriculography at our institution within 30 days. The exclusion criteria for both groups were as follows: previous diagnosis of CAD, submaximal exercise, over 75 years old, inability to reach 85% of their age-predicted maximum heart rate, presence of atrial fibrillation or flutter, history of coronary artery bypass graft surgery, previous myocardial infarction, percutaneous coronary intervention, slow coronary flow, chronic obstructive pulmonary disease, any systemic disease, congestive heart failure, any acute coronary syndrome, moderate to severe valvular disease, and the use of beta blocker (BB) medication, digoxin, calcium channel blockers, nitrates or other anti-ischemic drugs.

Variables

Exercise performance variables were as the follows: resting and peak blood pressure, resting and peak heart rate, heart rate recovery, ST depression, Duke score, heart rate reserve, functional exercise capacity (metabolic equivalent: METS), and Gensini score. Duke Treadmill Exercise Score was calculated as exercise time-[(5 x max ST deviation)-(4 x treadmill angina index)]. The other independent study variables assessed were age, body mass index (BMI), gender, diabetes mellitus, hypertension, and dyslipidemia. BMI was calculated by dividing body weight by height squared (kg/m^2). Hypertension, diabetes mellitus and dyslipidemia were defined in accordance with previously reported medical literature (12-14). CAD was defined as >50% diameter stenosis in at least one major coronary artery.

Exercise test and heart rate recovery

The Bruce protocol was used for TET and the sitting position was used during the cool-down period after exercise. The lead system consisted of the Mason-Likar modification of the standard 12-lead system. Continuous ECGs were digitally recorded and stored at 500 Hz using the CardioSoft exercise ECG system (version 4.14, GE Healthcare, Freiburg, Germany). Heart rate and blood pressure were recorded and ECGs were performed before and immediately after exercise. Post-exercise HRR was measured in the sitting position during the cool-down period after the cessation of peak exercise. HRR was obtained by subtracting heart rate at the first minute from the peak heart rate obtained during exercise. Abnormal HRR1 was deemed to be ≤21 beats at the first minute after the recovery phase, as previously described by Georgoulias et al. (15). Abnormal HRR1 was used as 12 or less beats at first minute upright position after exercise for protocols that a 2-minute post-exercise cool-down at 1.5 mph and 2.5% grade in most previous studies (1, 2, 4, 8).

Angiographic assessment

Selective coronary angiography (Integris, Philips Medical Systems, Eindhoven, Netherlands) was performed via the femoral artery using the Judkins technique. Angiographic characteristics were determined via a comprehensive review of the angiogram. The presence of CAD was defined by quantitative coronary angiography and the subjects were divided into two groups based on the presence (>50%) or absence (<50%) of stenosis in a major epicardial coronary artery. The Gensini scoring system (16), is a reliable system for determining the severity of coronary stenosis, and the number of coronary artery involvements were used to calculate the severity of CAD. The degree of coronary artery stenosis was evaluated according to the consensus opinion of three experienced interventional cardiologists.

Statistical analysis

All statistical analyses were performed using the SPSS version 17 (SPSS Inc., Chicago, IL, USA) software package. The normality of the distribution of all continuous variables was assessed using the Kolmogorov-Smirnov test. Data were expressed as mean±standard deviation (SD) for normally distributed data, and median for abnormally distributed data. Mean differences for continuous variables between the two groups were assessed using the independent Student's t-test and Mann-Whitney U test. Categorical variables such as gender, diabetes, hypertension, smoking and abnormal HRR in the control and CAD groups were compared using the chi-square test. For the prediction of CAD, receiver operating characteristic (ROC) analysis was performed using Metlab software(Version 12.5.0, Ostend, Belgium), to identify the impaired HRR value and found ≤21/beats as the best specificity and sensitivity point for predicting CAD. Odds ratios (OR) were calculated and the results are presented as ORs with a 95% confidence interval (CI). After entering univariate predictors into multivariate models, logistic regression analysis was performed to evaluate the independent predictors of abnormal HRR. Spearman's rank correlation analysis was performed to investigate whether there was a correlation between HRR and Gensini score. A p value of <0.05 was deemed to indicate statistical significance.

Results

Demographic features

A total of 200 subjects (124 men and 76 women) aged 33 to 75 years were enrolled in the study. Mean ages of the control and CAD groups were 57.0±9.4 and 57.5±8.1 respectively, and did not differ significantly (p=0.125). There were 41 (58.6%) and 83 (63.8%) males in the control and CAD groups respectively, which did not represent a significant gender difference (p=0.446) (Table 1).

Table 1. Demographic characteristics, risk factors, biochemical and exercise performance data of patients classified to CAD and control groups

Variables	CAD group n=130	Control group n=70	*P* value	Confidence interval
Male gender, n (%)	83 (63.8)	41 (58.6)	0.466[c]	-0.19 to 0.09
Age, years	57.5±8.1	57±9.4	0.125[b]	-0.54 to 4.47
BMI, kg/m^2	28.5±3.7	28.7±4.6	0.326[b]	-1.26 to 1.10
Diabetes, n (%)	42 (32.3)	15 (21.4)	0.164[c]	-4.8 to 54.5
Dyslipidemia, n (%)	41 (31.5)	22 (31.4)	0.934[c]	-0.10 to 0.12
Hypertension, n (%)	41 (31.5)	25 (35.7)	0.551[c]	-0.18 to 0.09
Smoking, n (%)	31 (23.8)	16 (22.9)	0.876[c]	-0.11 to 0.13
Fasting glucose, mg/dL	111 (67-326)	104 (67-266)	0.111[a]	-2.48 to 23.7
LDL, mg /dL	138±41	131±44	0.168[b]	-3.68 to 20.9
HDL, mg/dL	42.7±9.7	47.9±12.6	0.01[b]	-8.3 to -2.02
Triglyceride, mg/dL	156 (44-497)	151 (38-436)	0.107[a]	-2.71 to 54.1
Resting SBP, mm Hg	138±20	138±19	0.551[b]	-5.43 to 10.08
Resting DBP, mm Hg	81.2±8.5	79.3±10.2	0.411[b]	- 1.87 to 4.52
Peak SBP, mm Hg	190±26	195±26	0.681[b]	-7.07 to 4.63
Peak DBP, mm Hg	86.7±4.5	92.3±13.5	0.018[b]	-11.4 to 1.28
Resting heart rate, bpm	82 (50-108)	85 (50-102)	0.06[a]	-8.6 to 0.22
Peak heart rate, bpm	141 (100-214)	152 (104-206)	0.001[a]	-19.7 to -7.3
Gensini scoring	29 (5-128)	3 (0-8)	0.001[a]	21.4 to 34.1
METs, unit	8.9±2.4	9.1±2.5	0.326[b]	-1.09 to 0.36
Heart rate reserve	59±19	68±21	0.002[b]	-15 to 3.3
ST depression, mm	1.47±0.92	1.41±0.71	0.661[b]	-0.19 to 0.30
Heart rate recovery	18 (4-56)	21 (3-53)	0.040[a]	-5.7 to -0.13

Data are presented as mean±SD, median (minimum-maximum) values and number/percentage, and 95% confidence interval; [c]Chi-square; [a]Mann-Whitney U test and [b]unpaired Student's t-tests, bpm-beat per minute BMI - body mass index; CAD - coronary artery diseases; HDL-high density lipoprotein; LDL - low-density lipoprotein; METs - metabolic equivalent, mm- millimeter

Table 2. Univariate logistic regression analysis of categorical variables according to HRR groups

Variables	Abnormal HRR (≤21 bpm) n=140	Normal HRR (21> bpm) n=60	*P*	Odds ratio	Confidence interval
Male gender, n (%)	87 (62.1)	37 (61.7)	0.949	1.02	0.55-1.92
Diabetes, n (%)[†]	47 (33.6)	10 (16.7)	0.017	2.52	1.17-5.42
Dyslipidemia, n (%)	40 (28.6)	23 (38.3)	0.175	0.64	0.34-1.21
Hypertension, n (%)[†]	52 (37.1)	14 (23.3)	0.047	1.95	1.02-3.86
Smoking, n (%)[†]	37 (26.4)	10 (16.6)	0.039	1.81	1.1-3.9
CAD presence, n (%)[†]	99 (70.7)	31 (51.7)	0.01	2.26	1.21-4.2
1- CVI, n (%)	40 (28.6)	18 (30)	0.838	0.93	0.48-1.81
2- CVI, n (%)	28 (20)	6 (10)	0.09	1.50	0.93-2.40
3- CVI, n (%)	30 (21.4)	8 (13.3)	0.185	1.21	0.91-1.60

[†]Variables included in multivariate logistic regression models for each end point. Data is presented number/percentage and odds ratio and 95% confidence interval; CAD - coronary artery disease; CVI - coronary artery involvement

CAD, Gensini score and cardiovascular risk factor distributions

CAD was evident in 130 subjects (65%). Gensini scores were significantly higher in the CAD group than in the control group [29 (5-128) vs. 3 (0-8), p<0.001]. The distributions of diabetes (p=0.164), smoking (p=0.876), dyslipidemia (p=0.934) and hypertension (p=0.551) in the two groups were similar. No significant differences in fasting glucose, low density lipoprotein cholesterol (LDL-C), or triglyceride values were evident between the two groups (all p values >0.05). Mean serum high density lipoprotein cholesterol (HDL-C) levels were significantly lower in the CAD group (p=0.01) as compared to the control group (Table 1).

Confounding clinical variables and the relationship between HRR and CAD

After adjustment for clinical variables such as age, gender, DM, HT, dyslipidemia and smoking between the two groups, the number of subjects with abnormal HRR was significantly higher in the CAD group (n=99, 70.7%) than in the control group (n=31, 51.7%), p=0.01 (Table 2). The subjects with CAD exhibited significantly lower mean peak heart rate, HRR, and heart rate reserve, but there were no significant differences in resting heart rate or METS values between the two groups (Table 1).

With regard to the frequency of abnormal HRR (≤21 beats) and normal HRR (>21 beats), abnormal HRR was evident in 140 subjects (70%). Diabetes, hypertension, smoking, CAD presence, resting and systolic blood pressure, resting and peak HR, and mean METS values were higher in the abnormal HRR group than in the normal HRR group. There were no differences in the number of major epicardial coronary artery involvements between the normal HRR and abnormal HRR groups (all p values <0.05) (Table 2). No significant differences were evident between the abnormal and the normal HRR groups with regard to age, BMI, fasting glucose, LDL-C, HDL-C, triglyceride levels, resting and peak diastolic blood pressure (BP), Gensini scores, ST depression or Duke treadmill scores (all p values >0.05) (Table 3).

Logistic regression analysis revealed that abnormal HRR was independently associated with the presence of CAD (OR=2.1, 95% CI: 1.1-3.9, p=0.02), diabetes (OR=1.6, 95% CI: 1.1-2.1, p=0.03), heart rate reserve (OR=0.96, 95% CI: 0.94-0.97, p<0.001), and peak heart rate (OR=1.01, 95% CI: 1.01-1.02, p=0.01), but not with hypertension, smoking, systolic BP or resting heart rate (Table 4). Additionally, HRR was not correlated with Gensini scores (r=-0.13, p=0.112) (Fig. 1).

HRR1 values were evaluated for the prediction of CAD via ROC analysis. HRR1 varied from 3-56 beats. The closest value of 21 beats or less to the best specificity and sensitivity point on the ROC curve was identified (Fig. 2). The diagnostic sensitivity, specificity, positive predictive and negative predictive values of HRR with regard to the prediction of CAD were 76.1%, 41.3%, 70.7% and 48.3% respectively.

Table 3. Baseline charecterisctics and exercise performance data of patients according to HRR groups

Variables	Abnormal HRR (≤21 beats) n=140	Normal HRR (21> beats) n=60	*P* value	Confidence interval
Age, years	58.6±8.4	57.5±9	0.389[b]	-1.47 to 3.77
BMI, kg/m^2	29.2±4.1	28.1±3.8	0.07[b]	-0.08 to 2.41
Fasting glucose, mg/dL	105 (73-295)	99 (67-326)	0.061[a]	-0.71 to 26
LDL, mg /dL	134±40	139±45	0.419[b]	-18.1 to 7.5
HDL, mg/dL	44±10	46±12	0.108[b]	-6.4 to 0.65
Triglyceride	150 (38-497)	134 (44-456)	0.646[a]	-20 to 31
Resting SBP, mm Hg[†]	141±20	136±19	0.04[b]	0.14 to 12
Resting DBP, mm Hg	80.4±8.6	79.5±10.3	0.421[b]	-1.78 to 3.42
Peak SBP, mm Hg[†]	196±25	187±27	0.01[b]	2.5 to 18
Peak DBP, mm Hg	88.7±4.7	91.9±12.9	0.07[b]	-8.9 to 1.01
Resting HR, bpm[†]	85 (59-102)	80 (50-108)	0.01[a]	1.5 to 10.5
Peak HR, bpm[†]	142 (100-214)	152 (100-206)	0.031[a]	-17 to -3.6
Gensini scoring	22 (0-128)	15 (0-112)	0.07[a]	-0.62 to 13
METs, unit[†]	8.6±2.4	9.6±2.4	0.01[b]	-1.8 to -0.3
Heart rate reserve[†]	56±18	74±20	<0.001[b]	-22 to -10
ST depression, mm	1.47±0.89	1.39±0.76	0.542[b]	-0.18 to 0.34
Mean Duke Score	-0.71 (-15.8-11.8)	-1.0 (-9.2-11.1)	0.293[a]	-2.3 to -0.7

[†]Variables included in multivariate logistic regression models for each end point. Data are presented as mean±SD, median (minimum-maximum) values and 95% confidence interval (CI); [a]Mann-Whitney U test and [b]Student's t-tests, BMI - body mass index, bpm-beat per minute; DBP - diastolic blood pressure; HDL - high density lipoprotein; HR - heart rate; LDL - low - density lipoprotein; METS - metabolic equivalent; SBP -systolic blood pressure

Table 4. Predictive variables of abnormal HRR1 ≤21 bpm on multivariate logistic regression analysis

Variables	*P*	OR (95% CI)
CAD presence	0.02	2.1 (1.1-3.9)
Diabetes	0.03	1.6 (1.1-2.1)
Heart rate reserve	0.001	0.96 (0.94-0.97)
Peak heart rate	0.01	1.01 (1.0-1.02)

CAD - coronary artery disease; CI - confidence interval; HRR1 - heart rate recovery at first minute; OR - odds ratio

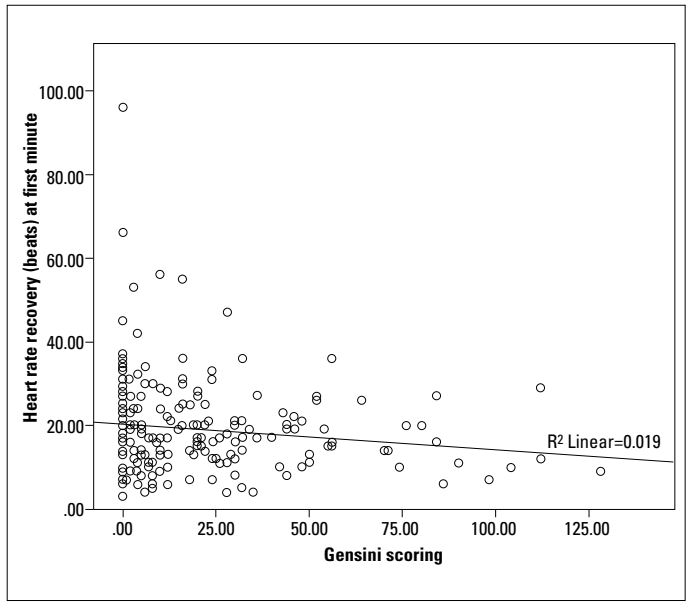

Figure 1. Shows no correlation between HRR and Gensini scoring

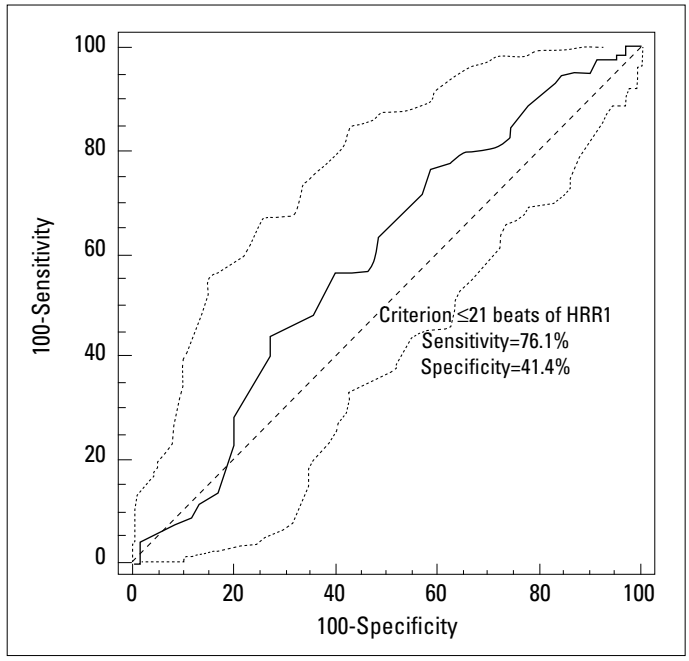

Figure 2. Diagnostic value of abnormal HRR ≤21 beats in prediction of CAD
Area under the ROC curve (AUC)=0.588, CI 95%: 0.517-0.657; p=0.039

Discussion

In this study, abnormal heart rate recovery (HRR1 ≤21 beats at first minute) response in the sitting position exhibited moderate sensitivity, but low specificity among the subjects who had an abnormal exercise ECG. In this data setting, there was no difference in terms of ST depression and METs between the CAD and the control group. An abnormal HRR1, thus, may provide incremental diagnostic information for the CAD presence in subjects with false positive exercise ECG. Our primary aim was to determine whether HRR could be implemented in the clinical setting to improve CAD diagnosis, not whether CAD is the mechanism responsible for abnormal HRR.

We measured HRR1 immediately after treadmill exercise in the sitting position. HRR1 ≤12 beats is widely accepted as abnormal in the upright position during the cool-down period (1, 2, 4, 8). Some studies have incorporated passive recovery (in the supine position), and most utilize a threshold of 18 beats at first minute (10, 17, 18). A cut off value of 21 beats for HRR1 was used by Georgoulias et al. (15). Currently, there are not enough data available on subjects who manifest an abnormal HR response in the sitting position during the post-exercise period. The sitting

position immediately after exercise is a passive recovery position. HRR1 might be slower in the sitting position than in the upright position due to the effect of relatively increased venous return, which stretches the right atrial wall and sino-atrial node.

According to most studies (9, 11, 19), HRR does not predict the existence or severity of CAD, but provides prognostic information for CAD patients. In our study there was no correlation between HRR and Gensini scores, or HRR and the number of coronary artery involvements, but there was a relationship between HRR and the presence of CAD. We also found that abnormal HRR is sensitive with regard to the diagnosis of CAD (76.1%), but does not exhibit good specificity (41.3%). These results are not similar to those reported by Vivekananthan et al. (6) who reported sensitivity of 31% and specificity of 76%. Most previous studies (1-3, 5-8, 10-11, 17), however, investigated either patients with heart failure, or patients with a previous myocardial infarction who were using BBs, calcium channel antagonists, and nitrates, which are likely to affect HRR. In our study, these factors were excluded because their impact on HRR is variable. Ghaffari et al. (10) was used HRR ≤18 beats as abnormal HRR1 in the supine position, and reported the sensitivity and specificity of HRR for detecting CAD to be 48.0% and 83.3%, respectively. Our study potentially suggest that abnormal HRR1 ≤21 beats in the sitting position immediately after exercise may be better predictive value for CAD presence than HRR1 ≤18 beats in the supine position and HRR1 ≤12 beats in the upright position in routine clinical practice.

Sufficient coronary blood flow is required for the maintenance of cardiac output during progressive treadmill exercise. Increased sympathetic neural stimulation due to exercise during TET can induce further coronary constriction, which can lead to myocardial ischemia, particularly in arterial segments narrowed by 70% or more. On the other hand, only a few studies have shown a relationship between myocardial ischemia detected by myocardial SPECT and HRR (15, 20). Georgoulias et al. (15) reported an HRR sensitivity of 73% and specificity of 76% for detecting myocardial ischemia, with regard to HRR of less than 21 beats with no cool-down period. However, they did not speculate about the exact mechanism by which CAD affects HRR. One could speculate that there is a strong association between myocardial ischemia and autonomic neuropathy (21).

Abnormal HRR is also highly dependent on chronotropic incompetence and it correlates with decreased heart rate reserve (22). We also found a relationship between HRR and chronotropic variables (peak heart-rate, heart-rate reserve), which is in accordance with previous studies (9, 22). HRR information, thus, can provide potentially additive diagnostic information related to chronotropic responses.

HRR is also markedly affected by factors such as age, smoking, diabetes, hypertension, heart failure, previous myocardial infarction, and chronic obstructive pulmonary disease (23, 24). In this study, age, gender, diabetes, smoking, hypertension, and dyslipidemia were similar in the two groups and all subjects had abnormal exercise ECG, thus the value deemed to indicate abnormal HRR (≤21 beats) in the sitting position may be considered to be a predictive factor for the presence of CAD.

Study limitations

The main limitation of the study of the present study was its size. We did not evaluate whether or not the subjects had metabolic syndrome as a variable because we evaluated most of its determinants (such as fasting glucose, HDL-C, triglyceride, and BP but the waist circumference).

Conclusion

According to our findings, a post-exercise abnormal HRR (≤21 beats) in the sitting position during a recovery cool-down period may be considered to have moderate sensitivity, but low specificity for predicting the presence of CAD, but HRR is a not predictive of the severity of CAD. ST segment depression, exercise angina, and functional capacity have already been shown to be more important in the diagnosis of CAD after TET. The calculation of HRR after TET will optimize not only the assessment of the prognosis of patients with CAD, but it may also provide potential information with regard to the presence of CAD. Our study potentially suggests that coronary angiography may be considered for routine incorporation when only abnormal HRR1 (≤21 beats) is present on TET in subjects with suspected for CAD.

Conflict of interest: None declared.

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