

# Relation between heart rate recovery index and syntax score

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## Abstract

**Background:** Heart rate recovery is a function of vagal reactivation, and its impairment is an independent prognostic indicator for cardiovascular and all-cause mortality. We aimed to search relationship between heart rate recovery after exercise stress test and SYNTAX score.

**Methods:** This was a single-center retrospective cohort study. 346 individuals were included. Heart rate recovery index (HRRI) is defined as the reduction in heart rate from the rate at peak exercise to the rate at the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> minutes after the cessation of the exercise stress test, and these results were indicated as HRRI1, HRRI2 and HRRI3 respectively. The SYNTAX scores were calculated for all patients. The SYNTAX score was divided into tertiles as low ( $\leq 22$ ), intermediate (23-32), and high ( $\geq 33$ ).

**Results:** Compared to control group, patients with impaired HRRI1 had significantly higher SYNTAX scores while HRRI2 and HRRI3 demonstrated a marginally significant relation with high SYNTAX score. In bi-serial and partial correlational analyses, HRRI1, HRRI2 and HRRI3 were positively correlated with the high SYNTAX score ( $r = -0.366, p < 0.001$ ;  $r = -0.313, p < 0.001$ ;  $r = -0.322, p < 0.001$ ). After adjustments were made for age, gender, hypertension, diabetes mellitus, hyperlipidemia and uric acid levels, HRRI1 was still significantly associated with high SYNTAX score ( $r = -0.236, 95\% \text{ CI}, p = 0.002$ ), while the relationships between the high SYNTAX score and HRRI2 and HRRI3 lost significance ( $r = -0.131, p = 0.091$ ;  $r = -0.159, p = 0.040$ ). ROC analyses showed HRRI 1,2 and 3 had moderate predictive ability for high SYNTAX score (AUC=0.713, 0.636-0.790, cut-off:22.5 bpm), (AUC=0.673, 0.593-0.752, cut-off:45.5 bpm) and (AUC=0.674, 0.594-0.764, cut-off:60.5 bpm) respectively with CI 95%.

**Conclusions:** A delayed decline of heart rate has been associated with increased risk of cardiovascular mortality. In our study lower heart rate recovery at first minute was associated with higher SYNTAX score.

## Introduction

Exercise stress testing, which is now widely available at a relatively low cost, is currently used most frequently to estimate cardiovascular performance. Basically, it is performed to identify angina or electrocardiographic changes induced by exercise. Determining exercise capacity, chronotropic response, heart rate reserve, heart rate recovery index and ventricular ectopic beats, increases the value of the test.

Heart rate recovery (HRR) is a function of vagal reactivation, and its deterioration is an independent prognostic indicator for cardiovascular events and all-cause mortality. HRRI is calculated by extracting the heart rates at 1, 2 and 3 minutes after cessation the test, from the patient's heart rate at finalizing the exercise. Many studies have shown that the HRRI in the 1st and 2nd minutes highly predicts prognosis in coronary artery patients and reported that those with impaired HRRI have a significantly higher risk of mortality [1-3].

SYNTAX score is an angiographic tool for grading the complexity of coronary artery disease according to the lesion number, lesion locations and functional importance. It was shown that SYNTAX scoring system could predict in-hospital, early and six months adverse cardiac outcomes [4,5]. Early prediction of mortality and morbidity enables taking precautions for complications in high risk patients.

In this study we aimed to search relationship between heart rate recovery index and SYNTAX score.

## Methods

This was a single-center retrospective cohort study approved by the relevant Ethics Committee. All consecutive candidates that had

had a coronary angiography within 30 days of exhibiting an abnormal exercise test result at our clinic, between January 2014 and December 2016, were enrolled. Of the subjects which we met the exercise test results on file scans, the ones reached the target heart rate were included in this study. The exclusion criteria were as follows: previous diagnosis of CAD, myocardial infarction, slow coronary flow, previous revascularization, over 75 years old, inability to reach 85% of their age-predicted maximum heart rate in exercise test, presence of atrial fibrillation or flutter, history of chronic obstructive pulmonary disease, congestive heart failure, moderate to severe valvular heart disease, and the use of beta blocker (BB) medication, digoxin or calcium channel blockers. According to our inclusion and exclusion criteria we collected data on 346 subjects who exhibited ST depression and reached at least 85% of the age-predicted maximal heart rate during treadmill exercise test. Baseline demographic, clinical, and angiographic characteristics data and stress test results were retrieved from the patient files and the electronic centralized clinical database of our center. All angiographic parameters were calculated by an experienced cardiologist who was blinded to the procedural data. The SYNTAX score was derived

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from the summation of the individual scores for each separate lesion producing  $\geq 50\%$  luminal obstruction in vessels  $\geq 1.5$  mm diameter.

The SYNTAX scores were calculated for all patients using dedicated software (available at <http://www.syntaxscore.com/calculator/start.htm>). Thereafter, the SYNTAX score was divided into tertiles as low ( $\leq 22$ ), intermediate (23-32), and high ( $\geq 33$ ).

All patients in the study had underwent exercise treadmill testing using the Bruce protocol. In our clinical applications, patients do not perform a cool-down walk and are placed supine as soon as possible after exercise. The predicted peak heart rate was calculated as  $(220 - \text{age})$ , and the aim was to reach at least 85% of the age-predicted heart rates. The end of exercise was tagged, and at least 3 minutes of post-exercise heart rate recorded with the subject at rest. Heart rate recovery indices were defined as the reduction in heart rate from the rate at finalizing exercise to the rate at the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> minutes after the cessation of the exercise stress test, and these results were indicated as HRR1, HRR2 and HRR3 respectively.

### Statistical analysis

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data

were described as mean  $\pm$  SD for normal distributions, and median (minimum – maximum value) for skewed distributions. Categorical data were described as number of cases (%).

While the differences in normally distributed variables among more than two independent groups were analyzed by One-Way ANOVA, otherwise, Kruskal Wallis test was applied for comparisons of the normally data. When the p-value from One-Way ANOVA or Kruskal Wallis test statistics were statistically significant post hoc LSD or Conover's non-parametric multiple comparison test were used to know which group differ from which others.

Univariate and multivariate logistic regression were used to determine predictors for SYNTAX score. Any variable having a significant univariate test at some arbitrary level is selected as a candidate for the multivariate analysis. We base this on the Wald test from logistic regression and p-value cut-off point of 0.25. Receiver Operating Characteristic (ROC) curve analysis was performed to detect the best sensitivity and specificity value of HRR1 in predicting SYNTAX score.

### Results

All patients and healthy participants had sinus rhythm and normal 12-lead ECG results at rest. The baseline characteristics of the study groups are shown in Table 1. Of the subjects, 251 (72.5%) were male, 228 (65.9 %) had hypertension, and 125 (36.1 %) had diabetes mellitus.

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

Variables	Control group <sup>c</sup> (n:87)	Lowest risk patients <sup>ci</sup> (syntax score $\leq$ 22) (n:80)	Intermediate risk patients <sup>cii</sup> (syntax score 23-32) (n:92)	Highest risk patients <sup>ciii</sup> (syntax score $\geq$ 33) (n:87)	Test statistic	p value
Male Gender, n (%)	49 (56.3)	62 (77.5)	80 (87.0)	60 (69.0)	22.635 <sup>t</sup>	<0.001
Age, year	55.01 $\pm$ 9.58	58.79 $\pm$ 8.20	63.85 $\pm$ 9.26	64.85 $\pm$ 9.55	21.806 <sup><math>\Phi</math></sup>	<0.001 <sup>a, b, c</sup>
BMI, kg/m <sup>2</sup>	29.13 $\pm$ 6.18	28.91 $\pm$ 3.87	28.05 $\pm$ 4.05	28.44 $\pm$ 3.98	0.961 <sup><math>\Phi</math></sup>	0.411
Diabetes, n (%)	13 (14.9)	29 (36.3)	42 (45.7)	41 (47.1)	25.099 <sup>t</sup>	<0.001
Hypertension, n (%)	42 (48.3)	49 (61.3)	68 (73.9)	69 (79.3)	22.385 <sup>t</sup>	<0.001
Hyperlipidemia, n (%)	31 (35.6)	55 (68.8)	55 (59.8)	56 (64.4)	25.445 <sup>t</sup>	<0.001
Smoking, n (%)	36 (41.4)	41 (51.3)	46 (50.0)	53 (60.9)	6.684 <sup>t</sup>	0.083
Uric acid, mg/dL	5.09 $\pm$ 1.35	5.66 $\pm$ 1.43	6.27 $\pm$ 1.69	6.19 $\pm$ 1.69	10.890 <sup><math>\Phi</math></sup>	<0.001 <sup>a, b, c, d, e</sup>
Ldl, mg/dL	130.77 $\pm$ 36.45	124.17 $\pm$ 39.60	115.23 $\pm$ 38.50	128.92 $\pm$ 39.04	2.947 <sup><math>\Phi</math></sup>	0.033 <sup>c, g</sup>
Hdl, mg/dL	45 (25-97)	40.51 (22-136)	38.85 (20.50-104)	40 (19.20-60.80)	15.124 <sup><math>\beta</math></sup>	0.002 <sup>a, b, c</sup>
Triglyceride, mg/dL	136 (47-513)	160.9 (50-379)	139.10 (34-528)	132 (51.43-496)	4.064 <sup><math>\beta</math></sup>	0.255
Cholesterol, mg/dL	204.02 $\pm$ 47.88	189.03 $\pm$ 42.68	182.11 $\pm$ 45.23	198.70 $\pm$ 44.76	4.158 <sup><math>\Phi</math></sup>	0.007 <sup>a, b, g</sup>
Fasting glucose, mg/dL	103.98 $\pm$ 19.29	111.74 $\pm$ 27.12	113.63 $\pm$ 33.60	134.77 $\pm$ 60.54	10.142 <sup><math>\Phi</math></sup>	<0.001 <sup>c, e, g</sup>
Creatinine, mg/dL	0.76 (0.07-5)	0.88 (0.56-7)	0.97(0.48-2.77)	0.95 (0.64-48)	46.494 <sup><math>\beta</math></sup>	<0.001 <sup>a, b, c</sup>
Duration of the exercise period,min	9.23 $\pm$ 5.77	8.17 $\pm$ 2.12	6.80 $\pm$ 3.52	7.04 $\pm$ 1.50	8.227 <sup><math>\Phi</math></sup>	<0.001 <sup>a, b, c, e</sup>
Resting SBP, mm Hg	120 (90-150)	120 (90-175)	120 (90-160)	130 (100-160)	12.933 <sup><math>\beta</math></sup>	0.005 <sup>c</sup>
Resting DBP, mm Hg	80 (50 -90)	80 (50-110)	80(50-100)	80 (50-100)	0.207 <sup><math>\beta</math></sup>	0.976
Peak SBP, mm Hg	160 (110-220)	160 (120-220)	160 (110-220)	170 (130-200)	5.002 <sup><math>\beta</math></sup>	0.172
Peak DBP, mm Hg	90 (60-110)	80 (9.90-110)	89 (9.90-110)	90 (60-110)	2.611 <sup><math>\beta</math></sup>	0.456
METs, unit	10.90 (3.59-14.80)	9.95 (5.20-129)	9.90 (4-13.91)	9.90 (4-13.91)	20.273 <sup><math>\beta</math></sup>	<0.001 <sup>b, c, d, e</sup>
Resting heart rate, bpm	79.97 $\pm$ 17.12	84.94 $\pm$ 16.68	83.85 $\pm$ 14.52	82.90 $\pm$ 16.44	11.077 <sup><math>\Phi</math></sup>	<0.001 <sup>a, b, c, d, e</sup>
Peak heart rate, bpm	148.82 $\pm$ 16.96	152.19 $\pm$ 15.25	146.62 $\pm$ 16.81	139.55 $\pm$ 16.75	9.409 <sup><math>\Phi</math></sup>	<0.001 <sup>c, d, e, g</sup>
HRR1, bpm	27.49 $\pm$ 10.54	26.46 $\pm$ 9.89	22.98 $\pm$ 7.74	20.46 $\pm$ 7.13	11.378 <sup><math>\Phi</math></sup>	<0.001 <sup>b, c, d, e</sup>
HRR2, bpm	47.60 $\pm$ 12.38	47.82 $\pm$ 14.25	43.96 $\pm$ 12.60	39.90 $\pm$ 11.09	7.499 <sup><math>\Phi</math></sup>	<0.001 <sup>c, d, e, g</sup>
HRR3, bpm	55.93 $\pm$ 14.28	53.39 $\pm$ 14.58	51.16 $\pm$ 13.48	47.15 $\pm$ 11.55	6.589 <sup><math>\Phi</math></sup>	0.001 <sup>b, c, e, g</sup>
ACE	6 (6.9)	12 (15.0)	12 (13.0)	10 (11.5)	2.975 <sup>t</sup>	0.396

Severity of coronary artery diseases was determined by SYNTAX Score. Data are expressed as mean $\pm$ standard deviation or median (minimum-maximum) for continuous variables and number (percentage) for categorical variables;  $\Phi$ : One way Anova test,  $\beta$ : Kruskal wallis test and t: Chi-square; least significant difference (LSD) or conover-Inman test were performed for the binary comparisons among the groups and the p value was set at 0.05. Significant differences were found between; a: C vs GI, b: C vs GII, c: C vs GIII, d: GI vs GII, e: GI vs GIII, g: GII vs GIII; BMI - body mass index; LDL - low-density lipoprotein; HDL - high density lipoprotein; SBP - systolic blood pressure; DBP - diastolic blood pressure; METs - metabolic equivalent; bpm - beat per minute; HRR1 - heart rate recovery index at first minute; HRR2 - heart rate recovery index at second minute; HRR3 - heart rate recovery index at third minute; ACE - accreditation for cardiovascular excellence; mm- millimeter.

All 346 subjects were categorized into 4 groups based on SYNTAX scores: control group, low ( $\leq 22$ ), intermediate (23-32), and high ( $\geq 33$ ) SYNTAX score. Significant differences for gender, DM and HT status were found between four groups. The binary comparisons of these four groups for HRR1, HRR2 and HRR3, also demonstrated statistically significant differences ( $p < 0.001$ ). Fasting glucose and serum creatinine levels, duration of the exercise period and the workload in METS were statistically significant in some of the binary comparisons. Univariate analyses of each risk factor for predicting SYNTAX scores were performed. Because of high correlation between HRR1, 2 and 3, influence of each of them was assessed separately. Any variable having a significant univariate test ( $p < 0.25$ ) was selected as a candidate for the multivariate analysis (Tables 2-4). Mean HRR1, 2 and 3 durations of control group and SYNTAX groups are shown in Figure 1. Mean reduction in heart rate declines as the severity of CAD increases. However, there were no statistically significant correlation between HRR1 indices and the low and intermediate SYNTAX scores. Univariate and multivariate analyses for HRR2 and HRR3 demonstrated a marginally significant relation with high SYNTAX score ( $39.90 \pm 11.09$  vs  $47.60 \pm 12.38$   $p = 0.067$  and  $47.15 \pm 11.55$  vs  $55.93 \pm 14.28$   $p = 0.063$  respectively) and analysis for HRR1 showed a statistically significant

relation ( $20.46 \pm 7.13$  vs  $27.49 \pm 10.54$   $p = 0.002$ ). Cardiovascular disease risk factors such as age, hypertension, uric acid level and diabetes mellitus also correlated with the high SYNTAX scores. To control their effects partial correlation analysis was performed (Table 5).

**Results of ROC analysis**

Figures 2, 3 & 4: ROC curve analyses for predictive values of HRR1 in detecting CAD severity evaluated by SYNTAX score. In the low SYNTAX ( $\leq 22$ ) group; no cut-offs were given for HRR1, HRR2 and HRR3 due to all of the asymptotic significances were greater than 0.5 (Figure 2).

In the intermediate SYNTAX group (23-32); asymptotic significance for HRR1 2 was greater than 0.5, so only cut offs for HRR1 and HRR3 were calculated (Figure 3). (AUC=0.627, 0.545-0.708, cut-off:22.5 bps) and (AUC=0.588, 0.504-0.671, cut-off:60.5 bps) respectively with CI 95%.

In the high SYNTAX group ( $\geq 33$ ); HRR1, 2 and 3 showed a moderate predictive ability for high SYNTAX score according to the area under the ROC curve (AUC=0.713, 0.636-0.790, with 75.9% sensitivity and 66.7% specificity, cut-off:22.5 bps), (AUC=0.673, 0.593-

**Table 2.** Univariate and multivariate analyses of HRR1 and variables associated with CAD in three SYNTAX groups

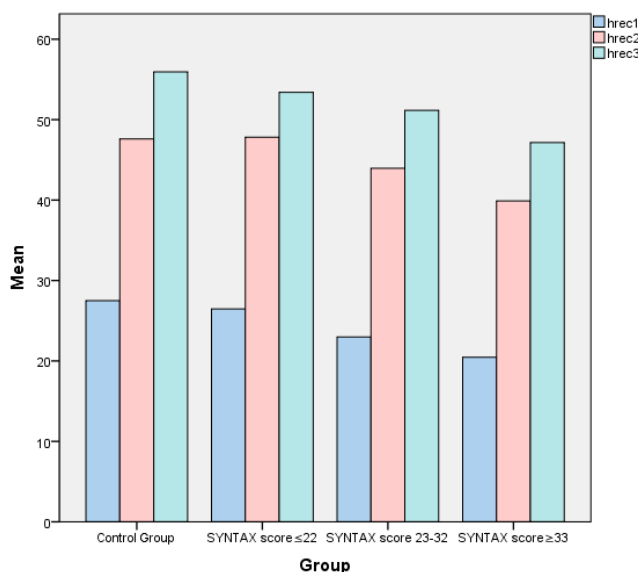
	Univariate Analysis				Multivariate Analysis			
	Wald	OR	%95 CI	P value	Wald	OR	%95 CI	P value
<b>Low (<math>\leq 22</math>) SYNTAX Score patients</b>								
Gender	8.153	2.671	1.361 to 5.243	0.004				
Age	6.889	1.049	1.012 to 1.087	0.009				
BMI	0.077	0.992	0.935 to 1.052	0.781				
Diabetes	9.546	3.237	1.536 to 6.819	0.002				
Hypertension	2.812	1.694	0.915 to 3.135	0.094				
Hyperlipidemia	17.580	3.974	2.085 to 7.575	<0.001				
Smoking	1.629	1.489	0.808 to 2.746	0.202				
Uric acid	6.508	1.350	1.072 to 1.699	0.011				
ACE	2.720	2.382	0.849 to 6.684	0.099				
HRR1	0.427	0.990	0.961 to 1.020	0.514				
<b>Intermediate (23-32) SYNTAX Score patients</b>								
Gender	18.933	5.170	2.467 to 10.836	<0.001	10.041	5.930	1.972 to 17.832	<b>0.002</b>
Age	27.353	1.105	1.064 to 1.147	<0.001	11.174	1.082	1.033 to 1.134	<b>0.001</b>
BMI	1.843	0.959	0.903 to 1.019	0.175	2.109	0.937	0.858 to 1.023	0.146
Diabetes	18.239	4.782	2.332 to 9.805	<0.001	6.885	3.582	1.381 to 9.290	<b>0.009</b>
Hypertension	12.041	3.036	1.621 to 5.684	0.001	3.735	2.352	0.988 to 5.599	0.053
Hyperlipidemia	10.236	2.685	1.466 to 4.918	0.001	1.672	1.714	0.757 to 3.878	0.196
Smoking	1.335	1.417	0.785 to 2.558	0.248	0.065	1.113	0.487 to 2.542	0.799
Uric acid	20.177	1.674	1.337 to 2.097	<0.001	12.177	1.657	1.248 to 2.201	<b>&lt;0.001</b>
ACE	1.811	2.025	0.725 to 5.658	0.178	3.896	4.057	1.010 to 16.295	<b>0.048</b>
HRR1	9.596	0.947	0.916 to 0.980	0.002	0.074	0.993	0.945 to 1.044	0.786
<b>High (<math>\geq 33</math>) SYNTAX Score patients</b>								
Gender	2.950	1.163	0.926 to 3.207	0.086	2.672	2.294	0.848 to 6.209	0.102
Age	29.458	1.115	1.072 to 1.160	<0.001	17.971	1.114	1.060 to 1.171	<b>&lt;0.001</b>
BMI	0.767	0.974	0.918 to 1.033	0.381				
Diabetes	19.313	5.074	2.459 to 10.468	<0.001	3.984	2.628	1.018 to 6.787	<b>0.046</b>
Hypertension	17.193	4.107	2.106 to 8.008	<0.001	3.163	2.240	0.921 to 5.447	0.075
Hyperlipidemia	13.956	3.263	1.755 to 6.069	<0.001	2.728	2.087	0.872 to 4.997	0.099
Smoking	6.561	2.208	1.204 to 4.049	0.010	2.425	2.012	0.835 to 4.848	0.119
Uric acid	17.920	1.620	1.296 to 2.025	<0.001	4.341	1.380	1.019 to 1.869	<b>0.037</b>
ACE	1.080	1.753	0.608 to 5.056	0.299				
HRR1	19.609	0.912	0.876 to 0.950	<0.001	9.789	0.910	0.858 to 0.965	<b>0.002</b>

CI (95 %); confidence; OR: odds ratio; Variable excluded of multivariate analysis since presented  $p > 0.25$  in univariate analysis.

**Table 3.** Univariate and multivariate analyses of HRR12 and variables associated with CAD in three SYNTAX groups

	Univariate Analysis				Multivariate Analysis			
	Wald	OR	%95 CI	P value	Wald	OR	%95 CI	P value
<b>Low (≤22) SYNTAX Score patients</b>								
Gender	8.153	2.671	1.361 to 5.243	0.004				
Age	6.889	1.049	1.012 to 1.087	0.009				
BMI	0.077	0.992	0.935 to 1.052	0.781				
Diabetes	9.546	3.237	1.536 to 6.819	0.002				
Hypertension	2.812	1.694	0.915 to 3.135	0.094				
Hyperlipidemia	17.580	3.974	2.085 to 7.575	<0.001				
Smoking	1.629	1.489	0.808 to 2.746	0.202				
Uric acid	6.508	1.350	1.072 to 1.699	0.011				
ACE	2.720	2.382	0.849 to 6.684	0.099				
HRR12	0.012	1.001	0.979 to 1.025	0.912				
<b>Intermediate (23-32) SYNTAX Score patients</b>								
Gender	18.933	5.170	2.467 to 10.836	<0.001	12.365	6.598	6.598 to 18.884	<0.001
Age	27.353	1.105	1.064 to 1.147	<0.001	11.747	1.085	1.085 to 1.137	0.001
BMI	1.843	0.959	0.903 to 1.019	0.175	1.991	0.939	0.939 to 1.025	0.158
Diabetes	18.239	4.782	2.332 to 9.805	<0.001	7.811	3.939	3.939 to 10.302	0.005
Hypertension	12.041	3.036	1.621 to 5.684	0.001	3.611	2.322	2.322 to 5.535	0.057
Hyperlipidemia	10.236	2.685	1.466 to 4.918	0.001	2.112	1.849	1.849 to 4.233	0.146
Smoking	1.335	1.417	0.785 to 2.558	0.248	0.016	1.056	1.056 to 2.442	0.898
Uric acid	20.177	1.674	1.337 to 2.097	<0.001	12.577	1.669	1.669 to 2.214	<0.001
ACE	1.811	2.025	0.725 to 5.658	0.178	4.096	4.158	4.158 to 16.527	0.043
HRR12	3.688	0.977	0.954 to 1.000	0.055	0.460	1.012	1.012 to 1.048	0.498
<b>High (≥33) SYNTAX Score patients</b>								
Gender	2.950	1.163	0.926 to 3.207	0.086	2.260	2.097	0.799 to 5.504	0.133
Age	29.458	1.115	1.072 to 1.160	<0.001	16.435	1.103	1.052 to 1.156	<0.001
BMI	0.767	0.974	0.918 to 1.033	0.381				
Diabetes	19.313	5.074	2.459 to 10.468	<0.001	4.491	2.814	1.081 to 7.327	0.034
Hypertension	17.193	4.107	2.106 to 8.008	<0.001	2.992	2.169	0.902 to 5.213	0.084
Hyperlipidemia	13.956	3.263	1.755 to 6.069	<0.001	3.028	2.118	0.910 to 4.932	0.082
Smoking	6.561	2.208	1.204 to 4.049	0.010	2.517	2.001	0.849 to 4.716	0.113
Uric acid	17.920	1.620	1.296 to 2.025	<0.001	5.777	1.436	1.069 to 1.930	0.016
ACE	1.080	1.753	0.608 to 5.056	0.299				
HRR12	15.474	0.945	0.919 to 0.972	<0.001	3.360	0.967	0.933 to 1.002	0.067

CI (95 %); confidence; OR: odds ratio; Variable excluded of multivariate analysis since presented p > 0.25 in univariate analysis.



**Figure 1.** Mean HRR1, 2 and 3 durations of control group and SYNTAX groups

**Table 4.** Univariate and multivariate analyses of HRR13 and variables associated with CAD in three SYNTAX groups

	Univariate Analysis				Multivariate Analysis			
	Wald	OR	%95 CI	P value	Wald	OR	%95 CI	P value
<b>Low (&lt;=22) SYNTAX Score patients</b>								
Gender	8.153	2.671	1.361 to 5.243	<b>0.004</b>				
Age	6.889	1.049	1.012 to 1.087	<b>0.009</b>				
BMI	0.077	0.992	0.935 to 1.052	0.781				
Diabetes	9.546	3.237	1.536 to 6.819	<b>0.002</b>				
Hypertension	2.812	1.694	0.915 to 3.135	<b>0.094</b>				
Hyperlipidemia	17.580	3.974	2.085 to 7.575	<b>&lt;0.001</b>				
Smoking	1.629	1.489	0.808 to 2.746	<b>0.202</b>				
Uric acid	6.508	1.350	1.072 to 1.699	<b>0.011</b>				
ACE	2.720	2.382	0.849 to 6.684	<b>0.099</b>				
HRR13	1.289	0.988	0.967 to 1.009	0.256				
<b>Intermediate (23-32) SYNTAX Score patients</b>								
Gender	18.933	5.170	2.467 to 10.836	<0.001	11.788	6.148	2.180 to17.337	<b>0.001</b>
Age	27.353	1.105	1.064 to 1.147	<0.001	11.208	1.082	1.033 to1.133	<b>0.001</b>
BMI	1.843	0.959	0.903 to 1.019	0.175	2.195	0.935	0.856 to1.022	0.138
Diabetes	18.239	4.782	2.332 to 9.805	<0.001	6.631	3.505	1.349 to9.107	<b>0.010</b>
Hypertension	12.041	3.036	1.621 to 5.684	0.001	3.880	2.424	1.004 to5.849	<b>0.049</b>
Hyperlipidemia	10.236	2.685	1.466 to 4.918	0.001	1.681	1.712	0.759 to3.861	0.195
Smoking	1.335	1.417	0.785 to 2.558	0.248	0.090	1.136	0.494 to2.613	0.765
Uric acid	20.177	1.674	1.337 to 2.097	<0.001	12.016	1.654	1.244 to2.197	<b>0.001</b>
ACE	1.811	2.025	0.725 to 5.658	0.178	3.624	3.889	.961 to15.742	0.057
HRR13	4.997	0.975	0.954 to 0.997	0.025	0.184	0.993	.959 to1.027	0.668
<b>High (&gt;=33) SYNTAX Score patients</b>								
Gender	2.950	1.163	0.926 to 3.207	0.086	2.819	2.288	0.871 to 6.015	0.093
Age	29.458	1.115	1.072 to 1.160	<b>&lt;0.001</b>	16.387	1.102	1.051 to 1.155	<b>&lt;0.001</b>
BMI	0.767	0.974	0.918 to 1.033	0.381				
Diabetes	19.313	5.074	2.459 to 10.468	<b>&lt;0.001</b>	5.052	2.974	1.150 to 7.693	<b>0.025</b>
Hypertension	17.193	4.107	2.106 to 8.008	<b>&lt;0.001</b>	4.137	2.457	1.033 to 5.844	<b>0.042</b>
Hyperlipidemia	13.956	3.263	1.755 to 6.069	<b>&lt;0.001</b>	3.831	2.307	.999 to 5.328	<b>0.049</b>
Smoking	6.561	2.208	1.204 to 4.049	<b>0.010</b>	2.120	1.889	.802 to 4.445	0.145
Uric acid	17.920	1.620	1.296 to 2.025	<b>&lt;0.001</b>	6.720	1.479	1.100 to 1.988	<b>0.010</b>
ACE	1.080	1.753	0.608 to 5.056	0.299				
HRR13	4.063	0.977	0.956 to 0.999	<b>0.044</b>	3.459	0.984	0.968 to 1.001	0.063

CI (95 %); confidence; OR: odds ratio; Variable excluded of multivariate analysis since presented p > 0.25 in univariate analysis.

**Table 5.** Bi-serial and Partial Correlation Analyses for HRR1 and SYNTAX Score Relationship

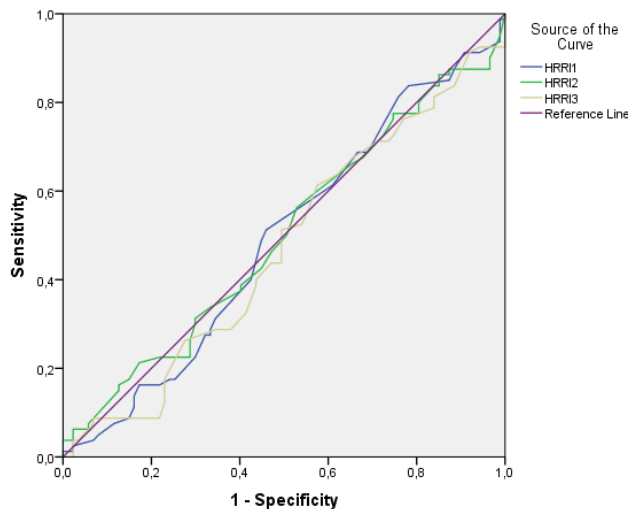
SYNTAX SCORE:	HRR11		HRR12		HRR13	
	r	p	r	p	r	p
<b>&lt;=22, (n:80)</b>						
None control variables	-0.051	0.516	0.009	0.912	-0.088	0.257
Control variables are age, gender,DM, HT, HL, uric acid	0.050	0.530	0.113	0.154	-0.007	0.930
<b>23-32, (n:92)</b>						
None control variables	-0.239	0.001	-0.145	0.053	-0.170	0.023
Control variables are age, gender,DM, HT, HL, uric acid	-0.023	0.761	0.030	0.693	-0.039	0.611
<b>&gt;=33, (n:87)</b>						
None control variables	-0.366	<0.001	-0.313	<0.001	-0.322	<0.001
Control variables are age, gender,DM, HT, HL, uric acid	-0.236	0.002	-0.131	0.091	-0.159	0.040

0.752, with 74.7% sensitivity and 52.9% specificity, cut-off:45.5 bps) and (AUC=0.674, 0.594-0.764, with 93.1% sensitivity and 41.4% specificity, cut-off:60.5 bps) respectively with CI 95% (Figure 4).

**Results of Correlation analysis**

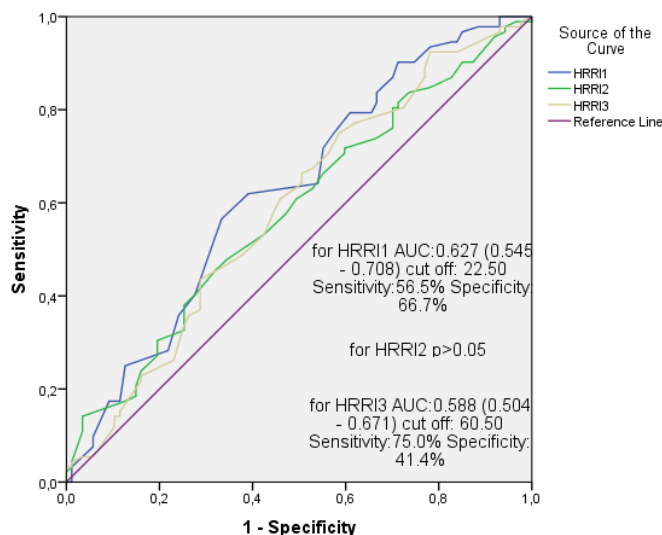
We also used point bi-serial correlation analysis to assess the relationship between HRR1 and SYNTAX score. No relationship was found between HRR11, HRR12 and HRR13 and the low SYNTAX score

(p=0.516, 0.912 and 0.257 resp). HRR11 and HRR13 had significant relationship (p=0.001 and p=0.023 respectively) and HRR12 had moderate relationship (p=0.053) with the intermediate SYNTAX score, however, the statistical significances were lost after partial correlational analysis, controlling for age, gender, hypertension, diabetes mellitus, hyperlipidemia and uric acid (p= 0.761, p= 0.693, p= 0.611 resp). HRR11, HRR12 and HRR13 were positively correlated with the high SYNTAX score (r = -0.366, p<0.001; r = - 0.313, p<0.001; r = -0.322,



**Figure 2.** Cut-off values for HRR1,2,3 in Low SYNTAX Score Group

In the low SYNTAX ( $\leq 22$ ) group; no cut-offs were given for HRR1, HRR2 and HRR3 due to all of the asymptotic significances were greater than 0.5.



**Figure 3.** Cut-off values for HRR1,2,3 in Intermediate SYNTAX Score Group

In the intermediate SYNTAX group (23-32); asymptotic significance for HRR2 was greater than 0.5, so only cut offs for HRR1 and HRR3 were calculated (Figure 3). (AUC=0.627, 0.545-0.708, cut-off:22.5 bps) and (AUC=0.588, 0.504-0.671, cut-off:60.5 bps) respectively with CI 95%.

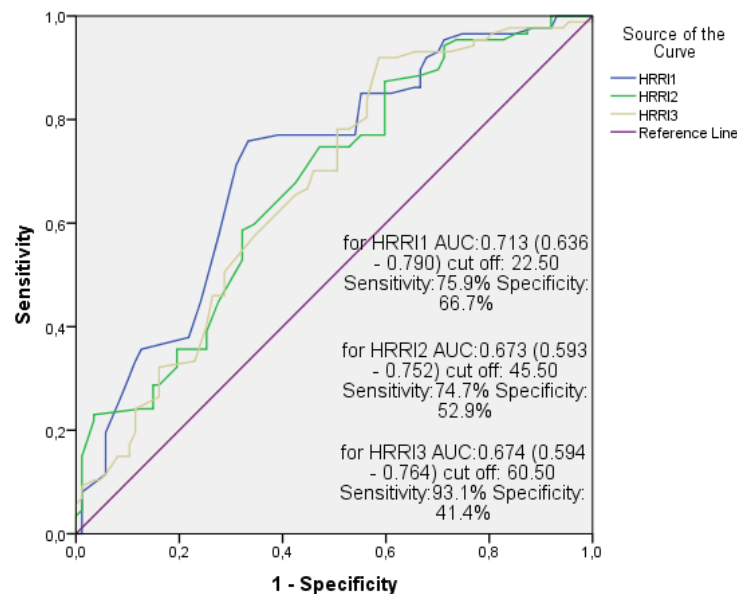
$p < 0.001$ ). After adjustment of all other independent variables, HRR1 was still significantly associated with high SYNTAX score ( $r = -0.236$ , 95% CI,  $p = 0.002$ ) while the relationships between the high SYNTAX score and HRR2 and HRR3 lost significance ( $r = -0.131$ ,  $p = 0.091$ ;  $r = -0.159$ ,  $p = 0.040$ ) (Table 5).

### Discussion

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in many developed countries [6]. Scientists and researchers have concentrated to reduce the burden by enhancing new identification and treatment strategies. Besides it is inexpensive and noninvasive, due to its reliability, exercise stress test is the initial test employed in the diagnosis of CAD. Exercise testing has been suggested to be valuable and less dependent on the patient's pre-test possibility for the purpose of risk stratification [7,8]. While evaluating a stress

test, ST segment deviation, exercise hypotension or hypertension, maximum exercise capacity, chronotropic response to exercise, heart rate variability and heart rate recovery are the parameters that have been shown to carry prognostic values [9-15]. Several studies have attempted to determine exercise test scores that incorporate clinical and demographic risk factors not based on the exercise test itself. An example of such is the Duke Treadmill Score. In a latest study by Dzenkeviciute et al., a negative correlation between Duke treadmill score and significant coronary artery stenosis ( $r = -0.181$ ,  $p = 0.005$ ), SYNTAX score ( $r = -0.173$ ;  $p = 0.007$ ), cardiac revascularizations ( $r = -0.213$ ;  $p = 0.001$ ) were found, however, its significance to predict cardiac revascularization was dependent on confounding clinical findings [16].

There is considerable recent evidence that heart rate recovery is an important parameter thought to reflect the cardiac autonomic nervous system function [17]. Changes in heart rate during and following exercise



**Figure 4.** Cut-off values for HRR1, 2, 3 in High SYNTAX Score Group

In the high SYNTAX group ( $\geq 33$ ); HRR1, 2 and 3 showed a moderate predictive ability for high SYNTAX score according to the area under the ROC curve (AUC=0.713, 0.636-0.790, with 75.9% sensitivity and 66.7% specificity, cut-off:22.5 bps), (AUC=0.673, 0.593-0.752, with 74.7% sensitivity and 52.9% specificity, cut-off:45.5 bps) and (AUC=0.674, 0.594-0.764, with 93.1% sensitivity and 41.4% specificity, cut-off:60.5 bps) respectively with CI 95% (Figure 4).

are determined by the balance between the excitatory sympathetic influence and the inhibitory parasympathetic influence. Sympathetic activity that increased during exercise reduces after finalizing exercise, however, recovery of the heart rate immediately after exercise is primarily a function of vagal reactivation, which is thought to be most important during the first minute after exercise [18]. In healthy and asymptomatic individuals, the heart rate falls rapidly within the first 30 seconds after exercise followed by a slower reduction [19]. In the case of presence of ischemia, ischemia-induced locally liberated adenosine, hydroxyl radicals and purinergic peptides can provoke modulations in both centripetal and centrifugal processing of intrathoracic nervous system [20]. Ischemia-induced cardio-cardiac reflexes and blunted baroreceptor reflexes result in dysfunction of cardiac autonomic nervous system and resulting deterioration of recovery of heart rate. Slower HRR1 rates denote a significantly higher risk of death. HRR1, which is a simple and non-invasive method for evaluating sympatho-vagal balance, is not routinely evaluated in daily clinical practice even though it is an independent risk factor for cardiovascular diseases.

Because depressed vagal tone is associated with cardiovascular death, we hypothesized that decreased HRR1 would be predictive of high SYNTAX score which is one of the major determinants of severity and mortality of CAD [21].

Airaksinen, *et al.* showed that cardiac vagal efferent activity is depressed in coronary artery disease even before the development of symptoms [22]. Also, a very rapid HR recovery immediately after exercise was found associated with lower risk of CHD and CVD events in a subanalysis of the Framingham Heart Study [1]. Vivekananthan, *et al.* [23] reported that HRR is an independent predictor of mortality along with angiographic severity of CAD, left ventricle function and exercise capacity.

Cole, *et al.* [24] studied 2428 adults who had been referred for exercise nuclear perfusion scans and they found that less than 12 bps

decrease in heart rate in the 1st minute after exercise was associated with a relative risk of 2.0 for death from any cause over a 6-year period after adjustment of other cardiac risk factors (95% confidence interval, 1.5-2.7;  $p < 0.001$ ). Current guidelines suggest that rapid supine patient placement after the exercise test offer advantages over other methods and should be considered [25]. A protocol with a staged cool-down walk was used in the aforementioned study. In our study, a protocol with prompt supine placement was used and ROC curve analysis determined the best cut-off value of HRR1 as 22.5 bpm, with 75.9% sensitivity and 66.7% specificity to predict severe (Syntax  $> 33$ ) score. In a study of Akyuz, *et al.* no correlation was found between HRR1 and Gensini scores and the number of coronary artery involvements, the only relationship was denoted between HRR1 and the presence of CAD [26]. In our study, HRR1 was directly correlated with high SYNTAX score which primarily defines severe CAD. Both after ROC curve analyses and partial correlation analyses adjusted for other possible confounders; HRR1 and HRR3 had significant, HRR2 had moderate predictive values for high SYNTAX scores in patients with CAD. The most likely mechanism by which severe CAD affects HRR1 is most likely due to the strong association between myocardial ischemia and cardiac autonomic dysfunction [18,20].

## Conclusion

Heart rate recovery can be defined as the rate at which the HR declines from either maximal or submaximal exercise to resting levels and has been identified as a powerful and independent predictor of cardiovascular and all-cause mortality in healthy adults. Our results point to the importance of the heart rate recovery in the identification of high CV risk patients and provides additional support for routine incorporation of heart rate recovery, at first minute, into standard risk stratification assessments among patients with suspected or documented CAD. Nevertheless, this is an observational and nonrandomized study; our results should be confirmed prospectively to confirm value of HRR1 to predict CAD severity.

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