Decreased heart rate recovery may predict a high SYNTAX score in patients with stable coronary artery disease

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ABSTRACT

An impaired heart rate recovery (HRR) has been associated with increased risk of cardiovascular events, cardiovascular, and all-cause mortality. However, the diagnostic ability of HRR for the presence and severity of coronary artery disease (CAD) has not been clearly elucidated. Our aim was to investigate the relationship between HRR and the SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score in patients with stable CAD (SCAD). A total of 406 patients with an abnormal treadmill exercise test and ≥50% coronary stenosis on coronary angiography were included. The HRR was calculated by subtracting the HR in the first minute of the recovery period from the maximum HR during exercise. The SYNTAX score ≥23 was accepted as high. Correlation of HRR with SYNTAX score and independent predictors of high SYNTAX score were determined. A high SYNTAX score was present in 172 (42%) patients. Mean HRR was lower in patients with a high SYNTAX score (9.8 ± 4.5 vs. 21.3 ± 9, $p < 0.001$). The SYNTAX score was negatively correlated with HRR (r: -0.580, $p < 0.001$). In multivariate logistic regression analysis, peripheral arterial disease (OR: 13.3; 95% CI: 3.120−34.520; $p < 0.001$), decreased HRR (OR: 0.780; 95% CI: 0.674−0.902; $p = 0.001$), peak systolic blood pressure (OR: 1.054; 95% CI: 1.023−1.087; $p = 0.001$), and peak HR (OR: 0.950; 95% CI: 0.923−0.977; $p < 0.001$) were found to be independent predictors of a high SYNTAX score. Our results showed that HRR is significantly correlated with the SYNTAX score, and a decreased HRR is an independent predictor of a high SYNTAX score in patients with SCAD.

KEY WORDS: Heart rate recovery; SYNTAX score; coronary artery disease; CAD; HRR

INTRODUCTION

An imbalance in the autonomic nervous system (ANS) contributes to cardiovascular pathology and increased cardiovascular mortality [1]. Heart rate recovery (HRR), measured after an exercise stress test (EST), represents a simple and useful tool for the assessment of cardiac autonomic activity, particularly parasympathetic tone. During exercise, increased sympathetic and decreased parasympathetic activity lead to increased HR. Immediately after the exercise, parasympathetic reactivation and subsequent sympathetic withdrawal occur, resulting in HR decrease (return to baseline) [2,3]. An abnormal HRR directly after exercise cessation has shown to be predictive of cardiovascular events and all-cause mortality in healthy and diseased individuals [4-6]. Moreover, slower baseline HRR was associated with risk factors for atherosclerosis, such as higher blood pressure and low-density lipoprotein cholesterol (LDL-C) levels [7]. However, other studies showed conflicting results regarding the diagnostic/predictive ability of HRR for the presence and severity of coronary artery disease (CAD), and the underlying mechanisms are yet to be characterized [2,8-11].

The SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score is an angiographic tool to determine the complexity of CAD [12]. The prognostic value of the SYNTAX score in predicting cardiovascular events, mortality, and morbidity in patients with CAD has been previously demonstrated [13,14] and the system shows several advantages compared to other scoring systems. For instance, the SYNTAX score can be used to assess

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the atherosclerotic burden but also to determine the number, location, complexity, and functional impact of obstructive lesions. The current guidelines on coronary revascularization recommend the use of the SYNTAX score to guide decision making between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients with CAD [15,16]. To the best of our knowledge, there is a lack of research on the relationship between HRR and the SYNTAX score in patients with CAD.

The aim of this study was to investigate whether HRR predicts a high SYNTAX score in patients with stable CAD (SCAD).

MATERIALS AND METHODS

This is a retrospective analysis of a multicenter observational study conducted between May 2017 and April 2018 in five coronary units in Turkey (Katip Celebi University School of Medicine, Çiğli State Hospital, Tepecik Training and Education Hospital and Tınaztepe Hospital in Izmir, and Manisa State Hospital in Manisa). Patients with SCAD who had an abnormal treadmill exercise test and ≥50% stenosis in coronary arteries, detected by coronary angiography, were included in the study. The patients underwent coronary angiography within two weeks of EST. All patients achieved 85% of age-predicted maximal HR.

The exclusion criteria were as follows: submaximal EST, history of prior acute coronary syndrome or coronary revascularization, arrhythmia, conduction block, heart failure, moderate or severe valvular disease, thyroid diseases, anemia, pacemaker implantation, or the use of antiarrhythmics, digoxin, nitrates, and drugs affecting the HR such as beta blockers, calcium channel blockers and ivabradine.

Exercise stress testing

After a fasting period of 6–12 hours, the patients underwent EST. None of the patients used rate control drugs before the test. The test was performed according to the Bruce protocol, in which the speed and gradient were increased at 3-minute intervals. Baseline blood pressure was recorded and a 12-lead electrocardiogram was performed before EST, and then at each exercise stage, peak exercise, and at 1-minute intervals during the recovery period. After peak exercise, patients maintained the upright position during an active cool-down for at least 2 minutes at a speed of 2.4 km/h and an inclination of 2.5%. The test was terminated in case of ≥1 mm ST segment elevation without Q wave, ≥2 mm horizontal or downsloping ST segment depression, a decrease in systolic blood pressure ≥10 mmHg, moderate to severe angina, malignant cardiac arrhythmia,

systolic blood pressure ≥250 mmHg or diastolic blood pressure ≥155 mmHg.

The functional capacity of patients during EST was estimated in metabolic equivalents [METs] (1 MET = 3.5 mL/kg per minute of oxygen consumption, which refers to the resting state). Other variables such as resting systolic and diastolic blood pressure, peak systolic and diastolic blood pressure, resting heart rate (RHR), peak HR and Duke Treadmill score (DTS): exercise time - [(5 × max ST deviation) - (4 × treadmill angina index)], were also obtained. The HRR was calculated by subtracting the HR in the first minute of the recovery period from the maximum HR during exercise.

Calculation of SYNTAX score

Standard coronary angiography was performed through the radial or femoral artery. At least 4 and 2 angiographic images were obtained for the left and right coronary systems, respectively. The coronary angiograms were evaluated by two independent experienced interventional cardiologists who were blinded to the clinical data and EST results of the patients. Coronary lesions with a lumen diameter >1.5 mm and at least 50% diameter stenosis were further analyzed. The SYNTAX score was calculated using the online SYNTAX score calculator 2.10 (www.syntaxscore.com). Patients were divided into two groups based on high (≥23) and low (<23) SYNTAX scores.

Clinical variables including the presence of diabetes mellitus, smoking, hyperlipidemia, chronic renal failure, peripheral arterial disease (PAD), hypertension and obstructive pulmonary disease were recorded. The baseline characteristics (age, gender, weight, and height) and laboratory parameters (uric acid level and leukocyte count) were also obtained.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, Version 15.0. (SPSS Inc., Chicago). Normal distribution of data was assessed by the Kolmogorov-Smirnov test. Continuous variables were reported as mean ± standard deviation (SD), median or interquartile range (IQR), and categorical variables were described as frequencies and percentages. The groups were compared using the independent Student's t-test and the Mann–Whitney U test for continuous variables and Chi-squared test for categorical variables. Correlation between SYNTAX score and HRR was analyzed using Spearman's rank correlation coefficient. Univariate and multivariate logistic regression (backward model) analysis was performed to determine the independent predictors of high SYNTAX scores. Variables with $p < 0.10$ in the univariate analysis were included in the multivariate logistic regression analysis. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

A total of 406 patients met the criteria and were included in the study. The mean age of the patients was 59 ± 8 years and the majority were male (79%). Clinical and demographic data of patients with high and low SYNTAX scores are shown in Table 1. The mean age, uric acid level, and the number of patients with family history of CAD, chronic renal failure, PAD and abnormal HRR values were higher in the group with a high SYNTAX score ($p < 0.05$). The number of major epicardial coronary arteries involved was also higher in patients with a high SYNTAX score ($p < 0.005$).

The EST findings are summarized in Table 2. All patients achieved at least 8 METs and 85% of the age-predicted maximal HR during EST. The mean HRR was lower in patients with a high compared to those with a low SYNTAX score (9.8 ± 4.5 vs. 21.3 ± 9, $p < 0.001$). Resting and peak diastolic and systolic blood pressures were higher in patients with a high SYNTAX score. Peak HR was lower in patients with a low SYNTAX score and RHR was higher in patients with a high SYNTAX score. The DTS and MET values were similar in both groups.

Univariate and multivariate predictors of the SYNTAX score are presented in Table 3 and 4, respectively. In the multivariate logistic regression analysis, PAD (OR: 13.3; 95% CI: 3.120−34.520; $p < 0.001$), decreased HRR (OR: 0.780; 95% CI: 0.674−0.902; $p = 0.001$), peak systolic blood pressure (OR: 1.054; 95% CI: 1.023−1.087; $p = 0.001$), and peak HR (OR: 0.950; 95% CI: 0.923−0.977; $p < 0.001$) were found to be independent predictors of the SYNTAX score.

A negative correlation of the HRR with the SYNTAX score (r: -0.580, $p < 0.001$) is shown in Figure 1.

DISCUSSION

HRR is a measure of ANS function. Attenuated HRR has been associated with increased risk of cardiovascular events and all-cause mortality [4-6]. Although slower HRR was associated with risk factors for atherosclerosis [7], conflicting results were reported on the diagnostic ability of HRR for the presence and severity of CAD [2,8-11]. In this study, we investigated whether HRR predicts a high SYNTAX score in patients with SCAD. We demonstrated a negative correlation between low HRR and high SYNTAX score, i.e., CAD patients with a high SYNTAX score had lower HRR. Furthermore, our multivariate logistic regression analysis showed that HRR as well as peak systolic blood pressure and peak HR were independent predictors of the SYNTAX score in patients with SCAD.

The SYNTAX score is a validated tool for the assessment of complexity and severity of CAD. It assists in determining the optimal revascularization strategy for patients with CAD and serves as a prognostic indicator of cardiovascular morbidity

TABLE 1. Baseline clinical and laboratory characteristics of patients with SCAD

Parameter	SYNTAX score <23 n=234 (58%)	SYNTAX score ≥23 n=172 (42%)	p
Age, years	58±8.6	61±9.1	<0.002
Gender, male	186 (79%)	128 (74%)	0.228
Weight	79±12	79±12	0.679
Height	169±8	168±8	0.257
BMI (kg/m²)	27.8±3.8	27.9±3.8	0.748
Cigarette smoking	98 (42%)	86 (50%)	0.104
Hypertension	122 (52%)	94 (55%)	0.616
Diabetes mellitus	89 (38%)	58 (34%)	0.372
Chronic renal failure	18 (8%)	52 (30%)	<0.001
Dyslipidemia	123 (53%)	94 (55%)	0.677
COPD	34 (14%)	28 (16%)	0.628
PAD	37 (16%)	44 (26%)	0.015
Ejection fraction	59±3.6	59±3.4	0.406
Coronary artery involvement			
LMCA involvement	12 (5%)	84 (49%)	<0.001
LAD involvement	160 (68%)	156 (91%)	<0.001
CX involvement	138 (59%)	134 (78%)	<0.001
RCA involvement	102 (44%)	102 (59%)	0.002
Single-vessel involvement	76 (32%)	18 (10%)	<0.001
Two-vessel involvement	104 (44%)	62 (36%)	0.076
Three-vessel involvement	42 (18%)	92 (53%)	<0.001
Prior antiplatelet treatment	43 (18%)	50 (29%)	0.011
Prior statin treatment	75 (32%)	51 (30%)	0.605
Leukocyte count (10⁹/L)	8.2±2.2	8.2±1.9	0.928
Uric acid (mg/dL)	5.7±1.3	6.8±2.3	<0.001

Results are presented as mean±SD, number (percentage) or percentage. SCAD: Stable coronary artery disease; SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; PAD: Peripheral arterial disease; LMCA: Left main coronary artery; LAD: Left anterior descending; CX: Circumflex; RCA: Right coronary artery

TABLE 2. Exercise stress test results in patients with SCAD in relation to the SYNTAX score

Parameter	SYNTAX score <23 n=234 (58%)	SYNTAX score ≥23 n=172 (42%)	p
Resting systolic blood pressure	136±19	163±25	<0.001
Resting diastolic blood pressure	82±3	108±19	<0.001
Peak systolic blood pressure	175±30	244±54	<0.001
Peak diastolic blood pressure	91±21	140±32	<0.001
RHR	84±14	88±14	0.017
Peak heart rate	146±22	99±27	<0.001
METs	11.5±1.6	11.7±2.5	0.249
Duke score	-4.5 (-9.75–(-1))	-6 (-12–(-1))	0.001
HRR	21.3±9	9.8±4.5	<0.001

Results are presented as mean±SD or median (IQR). SCAD: Stable coronary artery disease; SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; RHR: Resting heart rate; HRR: Heart rate recovery; IQR: Interquartile range; MET: Metabolic equivalent

TABLE 3. Predictors of high SYNTAX score in patients with SCAD according to univariate logistic regression analysis

Parameter	OR	95% CI	p
Age	1.036	1.012–1.059	0.002
Cigarette smoking	1.388	0.934–2.062	0.105
Chronic renal failure	5.2	2.910–2.293	<0.001
PAD	1.830	1.121–2.989	0.016
Abnormal HRR	30.252	17.557–52.127	<0.001
Uric acid	1.374	1.196–1.579	<0.001
Resting systolic blood pressure	1.054	1.042–1.066	<0.001
Resting diastolic blood pressure	1.065	1.053–1.1078	<0.001
Peak systolic blood pressure	1.031	1.025–1.036	<0.001
Peak diastolic blood pressure	1.050	1.040–1.061	<0.001
RHR	1.018	1.003–1.033	0.018
Peak heart rate	0.941	0.931–0.951	<0.001
Duke score	1.011	0.988–1.035	0.358

SCAD: Stable coronary artery disease; SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; PAD: Peripheral arterial disease; RHR: Resting heart rate; HRR: Heart rate recovery; CI: Confidence interval; OR: Odds ratio

TABLE 4. Predictors of high SYNTAX score in patients with SCAD according to multivariate logistic regression analysis

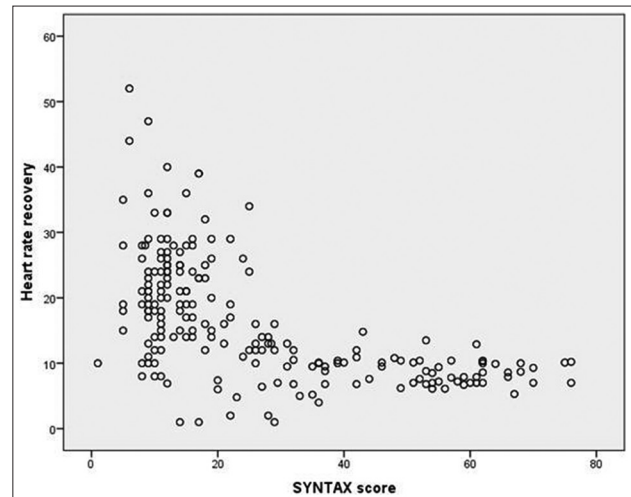| Parameter	OR	95% CI	p
PAD	13.3	3.120–34.520	0.001
HRR	0.780	0.674–0.902	0.001
Peak systolic blood pressure	1.054	1.023–1.087	0.001
Peak heart rate	0.950	0.923–0.977	<0.001

SCAD: Stable coronary artery disease; SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; PAD: Peripheral arterial disease; HRR: Heart rate recovery; CI: Confidence interval; OR: Odds ratio

FIGURE 1. A negative correlation of heart rate recovery (HRR) with SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score in patients with stable coronary artery disease (r: -0.580, $p < 0.001$).

EST parameters have also been related to the severity of CAD. In the current study, both resting and peak blood pressure were higher in patients with a high SYNTAX score. These patients may have had uncontrolled hypertension, where higher baseline systolic and diastolic blood pressure led to an exaggerated systolic and diastolic blood pressure response during EST, as demonstrated previously [20]. The DTS has been negatively correlated with the SYNTAX score [21,22], although the correlation coefficients varied greatly between different studies. For example, in 65 patients with a positive exercise test and who underwent coronary angiography, Acar et al. [21] found a strong negative correlation between the DTS and SYNTAX score (r = -0.91, $p < 0.001$). On the other hand, in a cohort of 258 patients with EST and coronary angiography, Dzenkeviciute et al. [22] demonstrated a weak correlation (r = -0.173; $p = 0.007$) between the two scores. Günaydın et al. [23] reported that the DTS was an independent predictor of a high SYNTAX score in 267 patients who underwent coronary angiography after a positive EST [23]. In our study, patients with a high SYNTAX score had a more negative DTS,

and mortality [17]. To date, various clinical and demographic variables have been associated with the SYNTAX score, including traditional cardiovascular risk factors such as advanced age, male gender, smoking history, and renal insufficiency [18]. Moreover, serum uric acid was shown to be an independent predictor of the complexity of CAD as evaluated by the clinical SYNTAX score (CSS) [19].

but the DTS was not a predictor of a high SYNTAX score according to the multivariate logistic regression analysis. There are several differences between our and the study of Günaydın et al. [23] which may explain the discrepancy in results. For example, in contrast to Günaydın study, our study population was larger (406 vs. 267 patients in Günaydın study), we included patients at higher cardiovascular risk, such as those with PAD and chronic renal failure, and we excluded patients with normal coronary arteries and noncritical stenosis (≤50%). Moreover, we analyzed a larger number of variables, including clinical variables, ANS and EST parameters, to determine independent predictors of a high SYNTAX score. These factors may have increased the accuracy of regression analysis for prediction of SYNTAX score in our study.

RHR is another measure of ANS function, and it was demonstrated that increased RHR, as well as decreased HR increment (maximum HR - RHR before exercise) and decreased HR decrement (maximum HR - RHR after exercise), are associated with the severity of CAD [24]. In another study including patients with SCAD, RHR was an independent predictor of SYNTAX score [25]. However, contrary to our study, Yılmaz et al. [25] did not exclude patients who were using HR-controlling medications such as beta blockers and calcium channel blockers. In the current study, the RHR was higher and peak HR was lower in patients with a high SYNTAX score, still only the peak HR was able to predict the SYNTAX score.

HRR is defined as a decrement in HR predominantly due to the reactivation of parasympathetic system after exercise cessation [2]. Georgoulias et al. suggested HRR 1 minute after peak exercise to be a reliable index of the severity of myocardial ischemia [26]. Moreover, an attenuated HRR has been related to CAD risk factors such as hypertension, diabetes mellitus and metabolic syndrome [27,28]. However, while some studies reported an association between abnormal HRR and the presence of CAD [8,9,11], other studies did not find a similar relationship [2,10]. These discrepancies may be explained by differences in study designs. First, exercise and recovery protocols varied between the studies. To allow a reliable comparison with previous studies, here we applied the most commonly used standard Bruce protocol with an active cool-down. Second, different tools for the assessment of the severity of CAD were utilized in those studies, such as the Gensini score and Duke CAD prognostic index. In the current study, we preferred to use the SYNTAX score to assess disease severity, as recommended by the current coronary revascularization guidelines [15].

To the best of our knowledge, the relationship between HRR and SYNTAX score has not been previously shown in patients with CAD. In this study, the difference in the mean HRR between high and low SYNTAX score groups was 11.5 beats. For 1 beat per minute increase in HRR, the hazard ratio for high SYNTAX score was 0.780 (95% CI: 0.674–0.902, $p = 0.001$). Although the study protocols and cut-off points for HRR differed between studies, the majority have demonstrated an increased risk of cardiovascular events in patients with an abnormal HRR. Indeed, even minor changes in HRR may affect cardiovascular outcomes. A meta-analysis including prospective cohort studies showed that for every 10 beats per minute decrements in HRR, the hazard ratio for cardiovascular events and all-cause mortality was 1.13 (95% CI 1.05–1.21) and 1.09 (95% CI 1.01–1.19), respectively in the general population. Moreover, their dose-response analysis suggested that the higher the HRR, the better the outcome [29].

The underlying mechanisms linking CAD presence/severity and abnormal HRR are not clear, although several explanations have been proposed [30-34]. Delayed postexercise HRR is mainly attributed to impaired vagal reactivation following exercise. Moreover, in patients who had myocardial infarction, the role of enhanced sympathetic activity at maximum exercise in the inhibition of parasympathetic reactivation after exercise was suggested, resulting in attenuated HRR [33]. Chronic sympathetic hyperactivity increases hemodynamic stress and cardiac workload which may lead to endothelial dysfunction and ultimately atherosclerosis. Conversely, increased parasympathetic activity has a protective effect by reducing HR and blood pressure [30]. Attenuated HRR may also increase myocardial oxygen consumption and have a deleterious effect on the myocardium [31]. Peçanha et al. [32] suggested a model for HRR in which the fast phase (a rapid decline in HR in the first minute of recovery promoted by vagal reactivation) is mainly determined by the deactivation of central command and mechanoreflex, while the slow phase (a more gradual decline in HR after the first minute due to an interaction of vagal reactivation and sympathetic withdrawal) is mediated predominantly by the metaboreflex and thermoregulatory deactivations [32]. The results of some studies suggested that HR response to central command activation in patients with CVD is increased at rest [34]. Similarly, mechanoreflex, metaboreflex and thermoregulation mechanisms may be impaired in CVD [32].

Several important limitations to the current study need to be considered. First, this was a retrospective study and the influence of unknown confounding factors cannot be ruled out. Second, we included only patients with at least 50% coronary stenosis, while those with abnormal EST and normal or insignificant coronary artery stenosis were excluded. Therefore, our results cannot be generalized to patients with abnormal EST results. Third, our results may be biased due to a limited set of criteria for patient selection and referral for coronary angiography. Future studies, of various designs and using the same EST protocol as in our study, should confirm

the validity and utility of HRR in predicting SYNTAX score in patients with CAD.

CONCLUSION

HRR is negatively correlated with the SYNTAX score in patients with SCAD. Decreased HRR may be used to predict high SYNTAX score in CAD patients.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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