



## Original Article

## The Relationship of Heart Rate Recovery Post Exercise Stress Test to Syntax Values in Patients with Stable Coronary Artery Disease

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## ARTICLE INFO

## ABSTRACT

## Keywords:

Coronary Artery Disease (CAD);  
Heart Rate Recovery (HRR);  
Syntax.

**Background:** The prognostic usefulness of abnormal heart rate recovery (HRR) as a predictor of death has been discovered 1–3. Abnormal HRR results from inadequate vagal activation after exercise 4,5. The association between HRR and angiography in CAD (coronary artery disease) has been studied, however the conclusions are still being contested due to a lack of data 6–8.

**Objectives:** The purpose of this study is to see if HRR after an EST (exercise stress test) may predict the severity of syntax values in individuals with stable CAD at Saiful Anwar Hospital Malang (RSSA).

**Methods:** This study is an analytic observational study. It was held in Saiful Anwar, Malang Hospital during January 2017–December 2019, including 366 patients. All patients underwent exercise stress test for CAD screening and coroner angiography. Those were divided into two groups, which included syntax score < 23 (n=148) and syntax score ≥ 23 (n= 218). Chi-square analysis was used to analyze the relationship correlation between HRR1, HRR2 and Syntax Score, and was used to compared between HRR1 (heart rate recovery first minutes), HRR2 (heart rate recovery second minute) and Syntax Score group. The confounding factor was adjusted with multivariate logistic regression analysis and AUC curve.

**Results:** There was a significant negative correlation between abnormal HRR1 and HRR2 after exercise and Syntax score, with strong correlation (HRR1 ; OR = -2.11, p = 0.00 AUC :90,8%, HRR2 ; OR = -1,6, p = 0,48, AUC : 70,4%).

**Conclusion:** Decrease HRR at first and second minutes after exercise stress test in stable CAD patient related to higher Syntax Score (>1).

## 1. Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and death globally, and its incidence is constantly rising<sup>9</sup>. In 2020, CAD contributed 26.4% of the total death rate in Indonesia. This figure is 4x higher than deaths from cancer (6%). Based on the diagnosis and symptoms, the highest estimated number of patients with CAD in 2013 was in East Java Province, with as many as 375,127 people (1.3%).<sup>10</sup>

The costs of diagnosing and treating CAD after symptoms manifestation are very high. Even when MSCT, MRI, and nuclear facilities improve, East Java still lacks a significant number of them. Therefore, it is crucial to eliminate risk factors before disease progression and to identify the presence of CAD through simple and applicable methods before the onset of symptoms.

Abnormal HRR (heart rate recovery) is caused by inadequate vagal activity during exercise, and its predictive significance for death has been shown.

Several studies have shown that an abnormal heart rate recovery cannot indicate the existence or severity of CAD based on the association between heart rate recovery and angiography in CAD. Nonetheless, Ghaffari et al. have revealed findings that contradict earlier research and imply that an aberrant HRR after exercise does predict the severity and prevalence of CAD. According to Lipinski et al., HRR2, defined as the decrease in heart rate from peak exercise speed to a rate two minutes after training stop, might indicate the occurrence of CAD.<sup>6,8,11</sup>

Coronary angiography is an important tool for quantifying the severity of coronary lesions. Several scoring systems were created to quantitatively assess the severity of coronary lesions angiographically.<sup>12</sup> One of the most widely used scoring systems in the literature today is the syntax score. A higher syntax score indicates the presence of a more complex lesion and is associated with more difficult management of the lesion. A higher syntax score is also associated with a poorer prognosis.<sup>13</sup>

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Table 1. Characteristic data of all subjects.

Variable	Syntax score		
	< 23, N : 148	≥ 23, N : 218	P
<b>Sex</b>			
Male	80,40%	84.4%	0,33
<b>Smoker</b>	54,70%	50,90%	0,52
HT	59,50%	63,30%	0,51
DM	29,7%	26,1%	0,47
CKD	4,90%	2,3%	0,32
Dyslipidemia	7%	7,1%	0,32
Age	52,9 ± 19,5	54,9 ± 18,72	0,051
BMI	28,4 ± 3,8	28,9 ± 28,3	0,12
METS	8,32 ± 2,32	6,91 ± 2,28	0,00
DTS	0,5 ± 7,43	-4,42 ± 6,75	0,00
HRR1	16,96 ± 4,93	8,39 ± 3,83	0,00
HRR2	31,69 ± 8,13	19,58 ± 5,57	0,00
Resting systole	123,02 ± 13,18	122,61 ± 14,60	0,78
Resting diastole	76,65 ± 10,49	75,85 ± 9,72	0,45
Peak systole	170,44 ± 23,27	151,10 ± 17,39	0,77
Peak diastole	93,98 ± 11,93	88,81 ± 8,77	0,85
Peak HR	144,26 ± 15,29	128,41 ± 20,30	0,93
ASA	17 (4,7%)	29 (7,9%)	
CPG	5 (1,4%)	12 (3,3%)	
TCG	6 (1,6%)	0	
ASA/CPG	97 (26%)	141 (38,6%)	
ASA/TCG	19 (5,2%)	35 (9,6%)	
ACEI/ARB	148 (40,4%)	218 (59,6%)	
B-blocker	138 (40,1%)	206 (59,9%)	
Statin	147 (40,8 %)	213 (59,2 %)	
<b>LM</b>			
Yes	33 (9 %)	82 (20,5%)	
No	115 (31,5%)	146 (39,9%)	
<b>LAD</b>			
Yes	109 (29,8%)	204 (55,8%)	
No	39 (10,6%)	14 (3,8%)	
<b>LCx</b>			
Yes	81 (22,1%)	170 (46,4%)	
No	67 (18,3%)	48 (13,1%)	
<b>RCA</b>			
Yes	86 (23,4%)	182 (73,2%)	
No	62 (16,9%)	36 (9,4%)	

Note. significant p value <0.05. HT = hypertension, DM = diabetes mellitus, CKD = Chronic kidney disease, BMI = Body mass index, Mets = Metabolic equivalent of task, DTS = Duke treadmill score, HRR1 = Heart rate recovery at first minute, HRR2 = Heart rate recovery at second minute, HR = Heart rate, ASA = Aspilet, CPG = Clopidogrel, TCG = Ticagerol, ACEI = Ace inhibitor, ARB = Angiotensin receptor blocker, B-blocker = Beta blocker, LM = Left main, LAD = Left anterior descending, LCx = Left circumflex, RCA = Right coronary arteries

This study aims to determine the relationship between heart rate recovery after EST as a predictor of the severity of syntax values in stable CAD patient at Saiful Anwar Hospital Malang (RSSA).

## 2. Methods

### 2.1 Study Design and Population

This research is a retrospective cross-sectional analytic observational study. From January 2017 to December 2019, medical record data was used to identify patients who underwent exercise stress test and coronary angiography. The target population in this study were all patients who underwent EST (exercise stress test) at dr. Saiful Anwar Malang's hospital. The affordable population in this study were patients who underwent EST and coronary angiography at Dr. Saiful Anwar Malang. The data was taken consecutively according to the sample selection criteria. Inclusion criteria included, age 18 – 74 years who underwent exercise stress test for CAD screening and coronary angiography at Saiful Anwar Hospital Malang with result of exercise

stress test positive ischemic response, and patients 3 months post ACS who were not revascularized. The data was validated by consultant cardiologist of prevention and rehabilitation. Exclusion criteria were patients dies during hospitalization, anemia, heart block, heart rate < 50 beats per minute, moderate to severe valvular disorders, post CABG patients, patient with pacemaker implantation.

### 2.2 Ethics

Management of research permits and the use of secondary data from patient medical records and coronary angiography in accordance with the procedures for research ethics permits and medical record services at RSUD dr. Saiful Anwar Malang.

### 2.3 Statistical Analysis

The data will be analyzed by the Statistical Package for the Social Science (SPSS) ver 25 software to determine the differences between variables.

Baseline characteristics were presented by means and standard deviation. Categorical variables were presented as percentages and frequencies and compared using Chi-square. Multivariate analysis using the logistic regression method and ROC curve was used to assess the strength of the relationship between variables.

### 3. Results

There were a total of 366 subjects who met the inclusion criteria, followed by data collection using medical record data and coronary angiography data at Dr. Hospital. Saiful Anwar Malang. This study evaluated the results of coronary angiography assessed using the SYNTAX score and compared the HRR after the exercise stress test at the first minute and at the second minute.

#### 3.1 Baseline Characteristic

There were 303 (82%) subjects were male and 63 (18%) subjects were female. The mean age of the study population was 53.2 ± 18.6 years with an age range of 29 - 77 years. Population anthropometric data showed a mean BMI of 28.4 ± 3.8 kg/m<sup>2</sup> (overweight mean). The highest risk factor was hypertension (61.7%) followed by smoking (52.5%). Most of the patients had syntax ≥ 23 with 218 patients and 148 patients had syntax <23.

Clinical and demographic data of patients with high and low SYNTAX scores are shown in Table 1. There were 303 (82%) subjects were male and 63 (18%) subjects were female. The mean age of the study population was 53.2 ± 18.6 years with an age range of 29 - 77 years. Population anthropometric data showed a mean BMI of 28.4 ± 3.8 kg/m<sup>2</sup> (overweight mean). The highest risk factor was hypertension (61.7%) followed by smoking (52.5%). Most of the patients had syntax 23 with 218 patients and 148 patients had syntax <23. Clinical and demographic data patients with high and low SYNTAX scores are shown in Table 3. DTS, HRR1, HRR2 and resting diastole were higher in the group with high SYNTAX scores (p < 0.05).

#### 3.2 Multivariate analysis

Univariate analysis for METS, DTS, HRR1 and HRR2 showed a significant association with high SYNTAX scores (6.91 ± 2.28 p=0.00, -4.42 ± 6.75 p=0.00, 8.39 ± 3.83 p=0.00, 19.58 ± 5.57 p=0.00, respectively) and there was also a significant relationship with a low SYNTAX score (8.32 ± 2.32 p= 0.00, 0.5 ± 7.43 p= 0.00, 16.96 ± 4.93 p=0.00, 31.69 ± 8.13 p = 0.00). The multivariate predictors of the SYNTAX score are presented in Table 2.

Table 2. Characteristics in groups with normal and abnormal FMD

	p	OR	95,0% C.I.	
			Lower	Upper
HRR1	.000	2.110	1.648	2.637
DTS	.024	2.038	1.100	2.776
HRR2	.027	1.604	1.118	1.967
Mets	.048	1.070	1.008	1.426

Note. \*) significant if the p-value is 0.05 or lower

In the multivariate logistic regression analysis, it was found that HRR1, HRR2, mets and DTS had a negative relationship with the syntax score.

#### 3.3 ROC Analysis Results

Figure 1 describes the ROC curve for predictive values of HRR1, HRR2 and DTS in detecting the severity of CAD which was evaluated by the SYNTAX score. At different threshold levels, the ROC

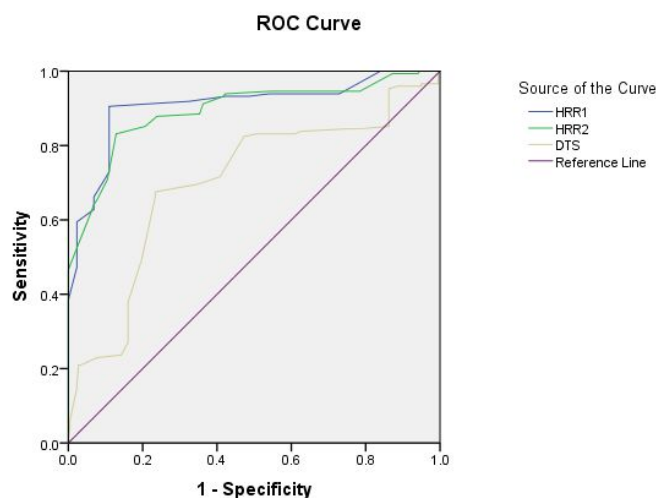


Figure 1. ROC curve of the relationship between HRR 1, HRR 2 and the Syntax score.

analysis plotted sensitivity on the y-axis and 1-specificity (false negative) on the x-axis. If the curve is near to the top vertical and horizontal axis lines, it represents high sensitivity and low false negative (1-specificity) or high specificity.

Table 3. AUC values of HRR1, HRR2 and DTS on syntax scores

Test Result Variable(s)	AUC	p	95% Confidence Interval	
			Lower Bound	Upper Bound
HRR1	.908	.000	.873	.942
HRR2	.704	.000	.644	.757
DTS	.893	.000	.857	.929

Note. \*) significant if the p-value is 0.05 or lower

Based on the ROC curve, it shows that the first minute recovery heart rate (HRR1) and second minute recovery heart rate (HRR2) have good diagnostic value, because the curve is far from the 50% line and close to 100%. The AUC values for HRR1, HRR2 and DTS obtained from the ROC method were 90.8% (95% CI: 87.3%-94.2%, p=0.000), 70% (95% CI: 64.4%-76.7%, with p=0.000), 89.3% (95% CI: 85.7%-92.9%, with p=0.000) respectively. Statistically, AUC values above 80% are considered significant, so HRR1 and DTS have significant values for predicting syntax scores in patients with stable coronary artery disease, while HRR2 has moderate values for predicting syntax scores.

### 4. Discussion

Coronary heart disease is a leading cause of morbidity and death in a number of affluent nations.<sup>14</sup> Scientists and researchers are always trying to reduce the burden of treating this disease by finding new ways to identify and treat coronary artery disease. Exercise stress test is not only inexpensive and non-invasive, but also has a high level of accuracy, so this test is often used as an initial test to diagnose CAD. Cardiac exercise testing is also frequently performed to assess risk stratification in patients with CAD. First minute recovery heart rate (HRR1) is one of the variables measured in the exercise stress test, and has been shown to be a predictor of mortality. Recent studies have shown that HRR1 can also be a predictor of coronary lesion severity.

From the demographic data in this study, it was found that the largest population was 82.4% male with an average a

ge of  $53.2 \pm 68$  years with the highest risk factor being hypertension. These data are consistent with research from Hata et al., they found that in the Asian population per 100,000 people there were 348 cases of CAD in men while in women there were 181 cases per 100,000 people, and hypertension was the largest risk factor.<sup>15</sup> The mean BMI in this population  $28.4 \pm 3.8$  kg/m<sup>2</sup> (obesity). In the study, Sadik et al also showed that the average BMI of patients undergoing exercise stress tests was overweight (27.8 for syntax score < 23 and 27.9 for syntax score 23).<sup>16,17</sup>

In this study, we found that HRR1 had a significant relationship with syntax scores. In this study we used a cut off of 12 bpm as a reference for heart rate recovery in the first minute and we got a p value < 0.000. Samad et al, conducted a study on 208 people (146 men, 66 women). They found that HRR1 had a significant relationship value ( $p < 0.001$ ).<sup>18</sup> Another study conducted by Sadik et al using a larger population of 406 patients, they also found that HRR1 had a significant relationship with the syntax score ( $p < 0.001$ ).<sup>16</sup> The study of Lipinski et al, found that the heart rate recovery was significantly affected by coronary artery stenosis, but that the heart rate recovery did not depend on the location of the coronary lesion.<sup>18</sup>

In multivariate analysis of HRR1 on syntax scores, we found that HRR1 had a significant negative relationship on syntax scores (OR = 2.11,  $p < 0.00$ ). Sadik et al's research also found that HRR1 also had a significant negative value on syntax (OR=0.78,  $p = 0.001$ ).<sup>16</sup> Cole et al showed that the decrease in heart rate after exercise stress test in the first minute was dominated by vagal activation. This is also reinforced by another study by Laurino et al, they found that there was a decrease in heart rate after the first minute of exercise which was suspected as a decrease in vagal activity in patients with stable coronary artery disease.

In this study, we also found that the second minute recovery heart rate after exercise had a significant relationship with the syntax value ( $p < 0.000$ ). This is in accordance with research conducted by Uzunget et al. They conducted a study on 346 people and found that the second minute recovery heart rate had a significant relationship with syntax ( $p < 0.001$ ).<sup>17</sup> Chen et al. also conducted a study of heart rate recovery from the first to the fifth minute in patients with stable coronary artery disease as assessed by the Genesis score. They found that heart rate from the first minute to the fifth minute heart rate had a significant relationship with the genesis score (HRR1 :  $p < 0.005$ , HRR2 :  $p < 0.008$ , HRR3 :  $p < 0.001$ , HRR4 :  $p < 0.002$ , HRR5 :  $p < 0.006$ ).<sup>19</sup>

In the multivariate analysis of the second minute recovery heart rate on syntax, we found that there was a significant negative relationship (OR=-1.60  $p = 0.027$  95% CI 11.1%-19.8%). Chen et al also found the same relationship (OR = -1.39  $p = 0.019$ ). They found heart rate recovery was significantly different in patients with >70% stenosis.<sup>19</sup> This result is also in line with the research conducted by Ghaffari et al.

The Duke treadmill score is one of the noninvasive modalities that has been known to be a predictor of coronary artery severity.<sup>8,20</sup> In this study, we found that the duke treadmill score had a significant negative relationship with the syntax value (OR: -2.03  $p = 0.024$  95% CI 11%-27.7%). This is also in line with other studies. Vilma et al. conducted a study of duke treadmill scores on syntax in 258 patients and found that the duke treadmill score predicts coronary artery severity ( $r = -0.181$  ;  $p = 0.005$ )<sup>8</sup>. Similar studies by Almeida et al also confirm this. In their study using 525 patients, the odds ratio of patients with abnormal angiography was 1.92.<sup>21,22</sup>

Based on the analysis of the ROC and AUC curves in this study, we found that the first minute recovery heart rate and the duke treadmill score both had strong values for predicting syntax scores (HRR1 ; 90.8% (95% CI: 87.3%) -94.2%, with  $p = 0.000$ ), DTS 89.3% (95% CI: 85.7%-92.9%, with  $p = 0.000$ ) This is in accordance with research conducted by Choi et al, they measured the heart rate recovery in the first and second minutes and the duke treadmill score on syntax. They found that the heart rate recovery in the first minute and the duke treadmill score had a positive linear relationship ( $R = 0.281$ ,  $p < 0.05$ )<sup>23</sup>.

This study has several limitations. First, this research is a cross-sectional study, which cannot prove the existence of causality between the variables studied. Second, this study is a single center study, the research subjects were obtained only at the Saiful Anwar regional hospital in Malang where the subject could not represent the population of stable coronary artery disease patients as a whole. Third, other factors that influence heart rate recovery such as hormonal disturbances, dyslipidemia, PAD, uric acid are difficult for us to obtain due to lack of data, so the results of this study require prospective studies to confirm the results of this study.

## 5. Conclusion

In summary, the HRR1 and HRR2 has a significant negative relationship to the syntax value in patients with stable coronary artery disease. HRR in the first minute after the exercise stress test has the same predictive value as the DTS in assessing the magnitude of the syntax value in patients with stable CAD.

## 6. Declarations

### 6.1. Ethics Approval and Consent to participate

This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involvement in the study.

### 6.2. Consent for publication

Not applicable.

### 6.3. Availability of data and materials

Data used in our study were presented in the main text.

### 6.4. Competing interests

Not applicable.

### 6.5. Funding source

Not applicable.

### 6.5. Funding source

Not applicable.

### 6.6. Authors contributions

Idea/concept: II, SA. Design: II, SA. Control/supervision: SA, CT, BS, VYP. Literature search: SA, CT, BS, VYP. Study quality assessment: SA, CT, BS, VYP. Data extraction: II, SA. Statistical analysis: II, SA. Results interpretation: DAI. Critical review/discussion: SA, CT, BS, VYP. Writing the article: II, SA. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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