

Exercise Test Related Heart Rate Recovery, Blood Pressure Response and Functional Capacity as Predictors for Coronary Artery Disease Severity

Qais Abdulla Adil^{1*}, Saleh Kamal Saleh²

Author's Information

1.M.B.CH.B., D.M, C.A.B.M,
F.I.C.M.S,
FABMS/cardiology
2.M.B.CH.B., C.A.B.M,
F.I.C.M.S/cardiology

Corresponding author:

Dr. Qais Abdulla Adil
qais.aaa@gmail.com

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ABSTRACT

Background: Exercise electrocardiographic testing is a fundamental and extensively utilized assessment for evaluating patients with cardiovascular disease (CVD). Variables from exercise tests outside the ST segment provide significant insights, especially when integrated with clinical data, to forecast outcomes and inform treatment across a diverse population, from healthy persons to those severely affected by heart disease.

Aim of study: To evaluate the predictive value of heart rate recovery, blood pressure response and functional capacity during exercise test for the presence of obstructive coronary artery disease.

Patients and method: An observational cross sectional study was conducted in Ibn Al Bittar Cardiac Centre in the period from January to August 2019, initially several hundreds of patients were included among those who were referred for exercise test (Bruce protocol) as part of the work up for the diagnosis of coronary artery disease, patients taking drugs affecting heart rate and those who are documented to have ischemic or other structural heart disease were excluded. Each patient was followed up until was subjected to coronary angiography, those who were not subjected to coronary angiography (according to the decision of the referring doctor) after four months from initial referral were excluded also. Finally, our study included 120 patients.

Results: only age was significantly associated with OCAD in univariate analysis. Twenty-one patients with OCAD (65.63%) were older than 50 years compared to 36.36% of patients without OCAD who had this age (OR= 3.34, 95%CI= 1.43-7.81, p= 0.004), DM, rest systolic BP and TMT score significantly associated with the presence of OCAD. the sensitivity and specificity of TMT score in detection of OCAD will be 78.13% and 88.64% respectively.

Conclusion: Heart rate recovery is poor predictor of OCAD. Elevated resting blood pressure can be a reliable evidence of uncontrolled hypertension and hence an independent predictor of OCAD. Functional capacity is a predictor of OCAD but not like the low TMT risk score which is an independent one.

Keywords: Exercise Test Related Heart Rate Recovery, functional Capacity, Coronary Artery Disease Severity

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1. INTRODUCTION

Muscle contraction and relaxation necessitate energy. The majority of this energy is obtained by oxidative metabolism to produce adenosine triphosphate; hence, energy demands at rest and during specific levels of physical activity (work rate) can be approximated using total-body oxygen absorption (VO₂) measurements (1,2). The Fick equation illustrates that VO₂ equals the product of cardiac output and peripheral oxygen extraction (i.e., arteriovenous oxygen difference) (3). VO₂ is readily articulated in multiples of resting oxygen demands (metabolic equivalents [METs]), where 1 MET represents resting energy expenditure, approximately equating to 3.5 mL O₂/kg body weight/min. This efficient technique quantifies the energy expended during specific physical activities in comparison to energy utilized during rest. Consequently, 5-MET exercise necessitates fivefold energy expenditure compared to resting levels (4). VO₂max is the maximum oxygen consumption attained during the execution of intense dynamic exercise that engages vast muscle groups, and by definition, it cannot be surpassed regardless of increases in workload. It pertains to age, gender, genetics, physical activity, and cardiovascular health. Cardiac output may elevate to four to six times its resting levels while in an upright position. Maximum cardiac output results from a twofold to threefold elevation in heart rate from baseline levels, accompanied by an increase in stroke volume (5,6).

2. METHODOLOGY

An observational cross sectional study was conducted in Ibn Al Bittar Cardiac Centre in the period from January to August 2019, initially several hundreds of patients were included among those who were referred for exercise test (Bruce protocol) as part of the work up for the diagnosis of coronary artery disease, patients taking drugs affecting heart rate and those who are documented to have ischemic or other structural heart disease were excluded. Each patient was followed up until was subjected to coronary angiography, those who were not subjected to coronary angiography (according to the decision of the referring doctor) after four months from initial referral were excluded also. Finally, our study included 120 patients. We divided our population into two groups according to the result of the coronary angiography the first group (patients group) those with OCAD and the second one (standard group) those without OCAD. Three variables from exercise test including heart rate recovery,

blood pressure response and functional capacity were studied and compared in between the two groups. Normal heart rate recovery at one minute to be defined by reduction in heart rate by ≥ 13 beats at one minute post exercise (7). Functional capacity for each patient measured by metabolic equivalents and classified according to their age and sex as low, fair, average, good or high as shown in **(Table 1)** (8). Blood pressure was measured before (rest or baseline BP) and throughout the test (at the end of each stage) and one minute at the recovery period, any decrease in systolic BP ≥ 10 mm Hg during exercise to be defined as hypotensive response and stop exercising. Those with baseline blood pressure of $\geq 140/90$ mm Hg considered with uncontrolled hypertension while those with normal baseline readings but their BP at the end of second stage $\geq 180/90$ mm Hg considered to have exaggerated blood pressure response (4,9).

Duke treadmill score was calculated for each of our patients from the equation;

Score = exercise time – (5 x ST deviation) – (4 x angina index)

Angina index is 2 when the chest pain forces patient to stop exercise, 1 if the patient can continue exercising in spite of the chest pain (mild) and 0 for no chest pain. Exercise time measured in minutes and ST deviation in millimeters (10).

The risk of having OCAD was assessed by the duke treadmill score as in **(Table 2)**.

Statistical analysis

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were expressed as mean \pm SD and analyzed with Student t-test. Categorical variables were expressed as number and percentage and analyzed with Chi-square test. Univariate and multivariate logistic regression was used to find out the association of each factors with the occurrence of OCAD. From this test the odds ratio (OR) and its corresponding confidence interval (95%CI) were calculated.

Table 1. Exercise capacity in mets according to age and sex

Age in years		Low	Fair	Average	Good	High
Females	20-29	< 7.5	8-10.5	10.5-12.5	12.5-16	>16
	30-39	< 7	7-9	9-11	11-16	>15
	40-49	< 6	6-8	8-10	10-14	>14
	50-59	< 5	5-7	7-9	9-13	>13
	60-69	< 4.5	4.5-6	6-8	8-11.5	>11.5
Male	20-29	< 8	8-11	11-14	14-17	>17
	30-39	< 7.5	7.5-10	10-12.5	12.5-16	>16
	40-49	< 7	7-8.5	8.5-11.5	11.5-15	>15
	50-59	< 6	6-8	8-11	11-14	>14
	60-69	< 5.5	5.5-7	7-9.5	9.5-13	>13

Table 2 Duke treadmill score

Duke score	< -11	-10 to 4	≥ 5
Risk of OCAD	high	intermediate	low

3. RESULTS

Our study included 120 patients, 76 (63.3%) males and 44 (36.6%) females, according to the result of the coronary angiography we divided them into the patient group (n=32) those with obstructive coronary artery disease and the standard group (n=88) those without OCAD.

The mean age of the patients with OCAD was 58.53±8.11 years which was higher than that of patients without OCAD (51.49±10.6 years) with highly significant difference. In contrast there were no significant differences between the two groups in BMI, gender distribution and smoking (**Table 3**). Although hypertension was more frequent among OCAD patients than those without OCAD (59.37% versus 52.28%), the difference was not significant. In contrast, the frequency of DM was significantly higher in patients with than those without OCAD (**Table 5**). The variation between the two groups regarding the frequency of dyslipidaemia and mild LV dysfunction was very small and far away from significant difference. Heart Rate and Blood Pressure Response to Exercise and Functional Capacity of the Study Population. Each of rest HR, peak HR and recovery HR were compatible between patients with OCAD (86.66±19.56

beat/min, 146.06±19.06 beats/min and 120.97±21.73 beats/min, respectively) and patients without OCAD (86.55±14.57 beats/min, 151.22±18.75 beats/min and 125.5±20.18 beats/min, respectively) with no significant differences. Rest systolic blood pressure was significantly higher among patients in the first group compared with the second group 150.56±25.32 mm Hg versus 132.23±19.43 respectively with a P value of 0.021, on the other hand the difference was not significant with regard to peak and recovery systolic BP. Patients with OCAD showed higher frequency of low functional capacity (18.75%) than those without OCAD (1.14%) with a highly significant difference. Likewise, moderate and high risk TMT score were more frequent in patients with OCAD (65.62% and 12.5%, respectively) than those in patients without OCAD (11.36% and 0%, respectively) with a highly significant difference (**Table 4**). Association of Demographic and clinical Characteristics with Obstructive Coronary Artery Disease. Of the four included demographic characteristics, only age was significantly associated with OCAD in univariate analysis. Twenty-one patients with OCAD (65.63%) were older than 50 years compared to 36.36% of patients without OCAD who had this age (OR= 3.34, 95%CI= 1.43-7.81, p= 0.004), as shown in (**Table 5**). DM was significantly associated with OCAD (OR= 3.06, 95%CI=1.27-7.22, p= 0.011). However, neither dyslipidaemia, hypertension nor left ventricular dysfunction was significantly associated with the disease. Association of Heart Rate and Blood Pressure responses, Functional Capacity and Duke TMT Score with Obstructive Coronary Artery Disease. In univariate analysis, rest systolic BP was significantly associated with OCAD. In this regard, 68.75% of patients with OCAD showed rest systolic BP greater than 140 mmHg compared to 36.36% of those without OCAD who had such BP (OR= 3.85, 95%CI= 1.62-9.14, p= 0.02). For some other parameters, like peak systolic BP, recovery systolic BP and recovery diastolic PB were, although the frequency of higher categories of these parameters were more frequent among OCAD patients than those without OCAD, the differences were not a significant. Low functional capacity (OR= 20.07(2.31-174.41, p<0.001), and moderate to high risk TMT (duke) score (OR=27.86, 95%CI= 9.6-80.87, p<0.001) were significantly associated with the presence of OCAD (**Table 6**).

All factors that had a significant association with OCAD were entered in a multivariate logistic regression model to differentiate between dependent and independent factors that are really associated with OCAD. The result of this model is illustrated in (**Table 7**). Each of age and

functional capacity had lost their significant association as independent factor, while DM, rest systolic BP and TMT score remained significantly associated with the presence of OCAD. Sensitivity and specificity of TMT score with its predictive values in detection of OCAD. By considering those with intermediate and low TMT score as those with positive test, there were 25 cases positive for OCAD by TMT score and coronary angiography, while there were 78 negative cases by both test. As such, the sensitivity and specificity of TMT score in detection of OCAD will be 78.13% and 88.64% respectively (**Table 8**).

Table 3. Demographic and clinical characteristics of the study population

Variable		With OCAD (n=32)		Without OCAD (n=88)		P. value
		No.	%	No.	%	
Age, years (mean \pm SD)		58.53+8.11	-	51.49+10.6	-	0.001
BMI, kg/m ² (mean \pm SD)		31.06+6.33	-	29.88+4.6	-	0.263
Gender	Male	20	48.78	56	63.64	0.909
	Female	12	51.22	32	36.36	
Smoking	Never	23	71.88	68	77.27	0.541
	Ex/current	9	28.12	20	22.73	
HTN	No	13	40.63	42	47.72	0.490
	Yes	19	59.37	46	52.28	
Diabetes	No	18	56.25	70	79.55	0.011
	Yes	14	43.75	18	20.45	
Dyslipidaemia	No	26	81.25	65	73.86	0.403
	Yes	6	18.75	23	26.14	
Lt ventricular function	Good	28	87.5	81	92.05	0.445
	Mild	4	12.5	7	7.95	
	dysfunction	-	-	-	-	

Table 4. Heart Rate and Blood Pressure Response to Exercise and Functional Capacity of The Study Population

Variable	With OCAD (n=32)		Without OCAD (n=88)		P. value	
	No.	%	No.	%		
Rest HR (beats/min)	86.66±19.56	-	86.55±14.57	-	0.973	
Peak HR (beats/min)	146.06±19.06	-	151.22±18.75	-	0.188	
Recovery HR (beats/min)	120.97±21.73	-	125.5±20.18	-	0.411	
Rest systolic BP	150.56±25.32	-	132.23±19.43	-	0.021	
Peak systolic BP	183.66±21.13	-	165.46±22.34	-	0.453	
Recovery systolic BP	175.62±25.63	-	170.21±23.17	-	0.381	
Functional capacity	Low	6	18.75	1	1.14	<0.001
	Fair to good	26	87.5	87	98.86	
TMT score	Low	7	21.88	78	88.64	<0.001
	Moderate	21	65.62	10	11.36	
	High	4	12.5	0	0.0	

Table 5. Univariate logistic regression for demographic and clinical characteristics

Variable	With OCAD (n=32)		Without OCAD (n=88)		P. value	OR (95%CI)	
	No.	%	No.	%			
Age	≤ 50	11	34.37	56	63.64	0.004	1.0 3.34 (1.43-7.81)
	>50	21	65.63	32	36.36		
BMI, kg/m ²	≤ 30	6	18.75	14	15.91	0.712	1.0 0.82 (0.29-2.36)
	>30	26	81.25	74	84.09		
Gender	Male	20	48.78	56	63.64	0.909	1.0 1.05 (0.46-2.43)
	Female	12	51.22	32	36.36		
Smoking	Never	23	71.88	68	77.27	0.541	1.0 1.33 (0.53-3.33)
	Ex/current	9	28.12	20	22.73		
Diabetes	No	18	56.25	70	79.55	0.011	1.0 3.06 (1.27-7.22)
	Yes	14	43.75	18	20.45		
Lt ventricular function	Good	28	87.5	81	92.05	0.445	1.0 1.65 (0.45-6.07)
	Mild dysfunction	4	12.5	7	7.95		
Dyslipidaemia	No	26	81.25	65	73.86	0.403	1.0 0.65 (0.24-1.79)
	Yes	6	18.75	23	26.14		
HTN	No	13	40.63	42	47.72	0.490	1.0 1.33 (0.59-3.03)
	Yes	19	59.37	46	52.28		

Table 6. Univariate logistic regression for heart rate, blood pressures, functional capacity and TMT risk score

Variable	With OCAD (n=32)		Without OCAD (n=88)		P. value	OR (95%CI)	
	No.	%	No.	%			
Rest HR (beats/min)	≤85	17	53.13	45	51.14	0.847	1.0 0.92(0.41-2.08)
	>85	15	46.87	43	48.86		
Peak HR (beats/min)	≤150	19	59.37	42	47.73	0.259	1.0 0.63(0.28-1.42)
	>150	13	40.63	46	52.27		
Recovery HR (beats/min)	≤120	17	53.13	41	46.59	0.526	1.0 0.77(0.34-1.73)
	>120	15	46.87	47	53.41		
Rest Systolic BP (mmHg)	≤140	10	31.25	56	63.64	0.02	1.0 3.85(1.62-9.14)
	>140	22	68.75	32	36.36		
Rest Diastolic BP (mmHg)	≤80	16	50.0	44	50.0	1.0	1.0 1.0(0.44-2.45)
	>80	16	50.0	44	50.0		
Peak Systolic BP (mmHg)	≤ 175	12	37.5	44	50.0	0.225	1.0 1.67(0.73-3.82)
	> 175	20	62.5	44	50.0		
Peak Diastolic BP (mmHg)	≤85	14	43.75	45	51.14	0.474	1.0 1.35(0.6-3.04)
	>85	18	56.25	43	48.86		
Recovery SBP(mmHg)	≤170	14	43.75	53	60.23	0.108	1.0 1.95(0.86-4.41)
	>170	18	56.25	35	39.77		
Recovery DBP(mmHg)	≤80	15	46.87	49	55.68	0.392	1.0 1.24(0.63-3.21)
	>80	17	53.13	39	44.32		
Functional capacity	Fair to good	26	87.5	87	98.86	<0.001	1.0 20.07(2.31-174.41)
	Low	6	18.75	1	1.14		
TMT score	Low risk	7	21.88	78	88.64	<0.001	1.0 27.86(9.6-80.87)
	Moderate to high risk	25	65.62	10	11.36		

Table 7. Multivariate logistic regression

Variable		P. value	OR(95%CI)
Age, years	≤ 50	0.48	1.0
	>50		1.62(0.43-6.08)
Diabetes	No	0.012	1.0
	Yes		5.39(1.45-20.12)
Rest Systolic BP (mmHg)	≤140	0.039	1.0
	>140		3.67(1.07-12.62)
Functional capacity	Fair to good	0.634	1.0
	Low		1.67(0.17-18.32)
TMT score	Low risk	<0.001	1.0
	Moderate to high risk		35.5(8.56-147.08)

Table 8. Sensitivity and specificity of TMT score in detection of OCAD

Variable		Coronary angiography		Total
		Positive	Negative	
TMT score	Positive	25	10	35
	Negative	7	78	85
	Total	32	88	120
Sensitivity = $25 / (25+7) \times 100 = 78.13\%$				
Specificity = $78 / (78+10) \times 100 = 88.64\%$				
Positive predictive value = $25 / (25+10) \times 100 = 69.44\%$				
Negative predictive value = $78 / (78+7) \times 100 = 91.76\%$				

4. DISCUSSION

Actually the heart rates of our patients recovered by more than 13 beats during the first minute in recovery period, a normal heart rate recovery set point used by previous studies and this may be explained by the fact that most of our population have good left ventricular function, or we may need to define a new set point for normal heart rate recovery regarding our patients, this why we divided our patients to those with recovery heart rate at 1 minute (RHR1) > 120 bpm {15(46.87%) of those with OCAD plus 47(53.41%) of those without OCAD}

and ≤ 120 bpm {17(53.13%) with OCAD plus 41(46.59%) without OCAD} P- value was 0.526 and odd ratio 1 so there was no significant alteration in heart rate recovery in patients with OCAD. Our study couldn't establish the association of abnormal heart rate recovery and the presence of obstructive coronary artery disease and this agrees with what Vivekananthan et al and Shetler et al found (11,12). Ghaffari et al. (13) have presented findings that contradict earlier studies, indicating that aberrant heart rate recovery post-exercise predicts the existence and severity of coronary artery disease (CAD). Furthermore, Lipinski et al. proposed that HRR2, characterized as the decline in heart rate from peak exercise to two minutes post-exercise cessation, may serve as an indicator of CAD existence (14). According to the findings by Akyüz et al., a post-exercise abnormal HR recovery may be considered to have moderate sensitivity, but low specificity for predicting the presence of CAD, but HR recovery is a not predictive of the severity of CAD (15). The studies that found impaired heart rate recovery in obstructive coronary artery disease (OCAD) may have been affected by the coexistence of other associated conditions like obstructive sleep apnea,(16) heart failure with preserved ejection fraction⁹ and type 2 diabetes mellitus (17).

We found in univariate analysis, rest (baseline) systolic BP, was significantly associated with OCAD. In this regard, 68.75% of patients with OCAD showed rest systolic BP greater than 140 mmHg compared to 36.36% of those without OCAD who had such BP (OR= 3.85, 95%CI= 1.62-9.14, $p= 0.02$) This aligns with the findings of Fagard and colleagues, who initially observed that neither submaximal nor maximal exercise blood pressure had additional predictive value beyond baseline blood pressure for cardiovascular disease or all-cause mortality in their study including 143 hypertensive men (18). For some other parameters, like peak systolic BP, recovery systolic BP and recovery diastolic PB were, although the frequency of higher categories of these parameters were more frequent among OCAD patients than those without OCAD, the differences were not a significant. In contrast, Allison et al., Filipovsky et al., and Mundal et al. discovered that elevated exercise blood pressure was linked to subsequent cardiovascular disease events, irrespective of resting blood pressure.(19-21) A recent analysis from the Framingham Offspring study revealed that diastolic blood pressure during low-level exercise (stage 2 Bruce protocol) was related with cardiovascular disease events, regardless of other risk variables and baseline blood pressure, while systolic blood pressure was not (22).

Sandra and colleague found that Bruce stage 2 blood pressure > 180/90 mm Hg identified non-hypertensive individual at higher risk of CVD events (23). In light of the contradictory results about the correlation with cardiovascular disease endpoints, the American College of Cardiology/American Heart Association guidelines on exercise testing recognized exercise-induced hypertension as an indicator for future clinical hypertension, although did not associate it with cardiovascular disease or death outcomes (24). With regard to exercise induced hypotension, all of our patients developed normal or exaggerated blood pressure response to exercise, this may be because no one of them have significant left ventricular dysfunction or three vessels disease (25). Decreases in systolic blood pressure during exercise stress testing correlate with left ventricular systolic dysfunction and the existence of severe obstructive coronary artery disease (26,27). Numerous studies indicate that a reduction in systolic blood pressure below baseline levels (exercise-induced hypotension) correlates with an elevated risk of cardiovascular incidents (28-30). Moreover, a heightened risk of cardiovascular mortality has been noted in men exhibiting modest maximal systolic blood pressure responses, as well as in patients with established hypertension and peripheral artery disease.(31) The American Heart Association recommends that a fall in systolic blood pressure over 10 mm Hg below resting levels is an unequivocal indicator for the cessation of exercise stress testing. Nonetheless, the research referenced that resulted in this suggestion have been confined to particular subpopulations predominantly comprising men.

We have found low functional capacity was significantly predictive of OCAD, 18.75% of patients with OCAD compared to 1.14% of those without OCAD had low functional capacity with a P- value of <0.001. This finding was agreed by each of Myers et al., Gulati et al. and others indicating that diminished exercise capacity (EC) correlates with an elevated risk of all-cause mortality and major adverse cardiovascular events (MACE) (32-37). The findings have been consistent across all ethnicities, genders, non-diabetic and diabetic individuals, as well as patients with left ventricular hypertrophy, as demonstrated by Pierre-Louis et al. and Alswat et al. (38,39). Finally, all factors that had a significant association with OCAD (age, diabetes, rest systolic blood pressure, functional capacity and TMT risk score) were entered in a multivariate logistic regression model to differentiate between dependent and independent factors that are really associated with OCAD. We found each of diabetes mellitus, high resting

systolic blood pressure and low TMT risk score are independent predictors of OCAD, for the diabetes mellitus we may say it is well known in association with CAD and to discuss this point is beyond the scope of this study. Elevated resting systolic blood pressure is a clue of poorly controlled hypertension and this is also well known in its role in atherosclerosis. Low functional capacity found not to be independent predictor of OCAD and this is accepted because it can be reduced by any non-cardiac illness or disease while low TMT risk score was independent predictor OCAD.

5. CONCLUSIONS

Heart rate recovery is poor predictor of OCAD. Elevated resting blood pressure can be a reliable evidence of uncontrolled hypertension and hence an independent predictor of OCAD. Functional capacity is a predictor of OCAD but not like the low TMT risk score which is an independent one. We recommend taking medical history and performing physical examination before the patient being engaged in the exercise test to avoid other illnesses or medications that may affect the functional capacity, heart rate or the blood pressure. Educate the patients that good control of hypertension minimizes the likelihood of OCAD. To get on more consistent results from the exercise test we recommend to calculate the Duke TMT risk score for all patients.

Ethical Approval:

All ethical issues were approved by the author. Data collection and patients' enrollment were in accordance with Declaration of Helsinki of World Medical Association, 2013 for the ethical principles of researches involving human. Signed informed consent was obtained from each participant and data were kept confidentially.

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