Abnormal heart rate recovery after treadmill stress testing; correlation with clinical, exercise testing and myocardial perfusion parameters in Diabetic patients versus non-Diabetics

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Abstract: **Background:** The increase in heart rate during exercise is considered to be attributed to sympathetic system activation combined with parasympathetic withdrawal. The prognostic importance of heart rate recovery 1 minute after exercise has already been established. **Aim of the work:** The aim of this study is to evaluate the degree of heart rate recovery after treadmill testing as an index of myocardial ischemia by focusing on the correlation between heart rate recovery and clinical, exercise testing and myocardial perfusion scanning parameters related to ischemia. **Material and methods:** a prospective study done over a period of one year that included 100 patients (50 diabetics and 50 non diabetics) aged 27-84 years The patients underwent single photon emission computed tomography myocardial perfusion imaging combined with symptom-limited exercise testing with technetium 99m sestamibi. The value for heart rate recovery was defined as the decrease in heart rate from peak exercise to 1 minute after termination of exercise. Nineteen beats per minute was defined as the lowest normal value for heart rate recovery. **Results**: We found 31 patients with abnormal heart rate recovery 14 patients in the non diabetic group and 17 patients in diabetic group. We also found a significant correlation between heart rate recovery 1 minute after exercise and stress myocardial perfusion results. Patients with an abnormal value of heart rate recovery were generally of an older age, were more likely men and had a higher frequency of risk factors for coronary artery disease. **Conclusion:** It seems that the heart rate recovery value 1 minute after peak exercise may be considered a reliable index of the severity of myocardial ischemia.

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1. Introduction:

Heart rate is normally determined by the pacemaker activity of the sinoatrial node (SA node) located in the posterior wall of the right atrium.

Heart rate is regulated by sympathetic and parasympathetic input to the sinoatrial node. The accelerans nerve provides sympathetic input to the heart by releasing norepinephrine onto the cells of the sinoatrial node, and the vagus nerve provides parasympathetic input to the heart by releasing acetylcholine onto sinoatrial node cells. Therefore, stimulation of the accelerans nerve increases heart rate, while stimulation of the vagus nerve decreases it. **(Schmidt-nielsen et al 1997).**

The increase in heart rate that accompanies exercise is due in part to a reduction in vagal tone. Cardiac output increase by four to six folds above basal levels during strenuous exercise in the upright position, depending on genetic endowment and level of training **(Hall 2010, Ingelsson et al 2007).**

Abnormal heart rate recovery refers to a relatively slow deceleration of heart rate following exercise cessation. This type of response reflects decreased vagal tone and is associated with increased mortality **(Froelicher et al 2006, Adabag et al 2008, Chaitman 2003, Morise 2004).**

Heart rate recovery (HRrecovery) is the reduction in heart rate at peak exercise and the rate as measured after a cool-down period of fixed duration. A greater reduction in heart rate after exercise during the reference period is associated with a higher level of cardiac fitness **(Froelicher et al 2006).**

Diabetes mellitus is a group of diseases characterized by insufficient production of insulin or by the failure to respond appropriately to insulin, resulting in hyperglycemia. Diabetes typically is classified as either type 2 diabetes, characterized by insulin resistance and relative insulin deficiency, representing greater than 90% of all diabetes cases, or type 1 diabetes, characterized by absolute insulin deficiency. Compared with nondiabetic persons, patients with diabetes have a two- to fourfold increased risk for development of and death from CHD **(Preis et al 2009).** Diabetes is associated with an increased risk for MI. Across the spectrum of acute coronary syndrome (ACS) events, in which diabetes may affect more than one in three patients,**(Fang et al**

2006, Gore et al 2012) those with diabetes have worse CVD outcomes after ACS events**(Wiviott et al 2008)**.

The purpose of this study is to evaluate heart rate recovery as an index of myocardial ischemia assessed by myocardial perfusion single photon emission computed tomography (SPECT) imaging which is a reliable method for assessing myocardial perfusion.

2. Material and methods:

This study include 100 patients (50 Diabetic and 50 non-Diabetic) were referred for symptom-limited exercise testing combined with single photon emission computed tomography (SPECT) myocardial perfusion imaging for evaluation of the presence or absence of ischemic heart disease from June 2015 to June 2016.

We excluded patients with a history of acute myocardial infarction within 2 days, high risk unstable angina patients, and patients with pre-excitation syndromes, atrioventricular block and those with an implanted pacemaker. We also excluded patients receiving digoxin and those with contraindication to or inability to perform treadmill testing because of a noncardiac condition (sciatica, disability and so on). Beta Blockers and calcium channel antagonists were discontinued 48 hours before and during the study. Nitrates were discontinued 24 hours before and during the study. Other antiarrhythmic medications were also discontinued (at least 48 hours before and during the study).

Hypertension was defined as a systolic blood pressure of 140 mm Hg or greater at rest and/or a diastolic blood pressure of 90 mm Hg or greater at rest, or treatment with antihypertensive medicines. Diagnoses of diabetes mellitus and lipid disorders were derived from the interviews with the patients and the use of corresponding medications.

After discontinuance of cardioactive medication and a 6 to 12-hour fast, the patients underwent symptom-limited tread treadmill exercise testing (Bruce protocol). a 12-lead electrocardiogram and blood pressure measurements were obtained at baseline, during each stage of exercise, at peak workload, and at 1-minute intervals for 5 minutes after exercise.

As a criterion of ischemic ST-segment response, we considered greater than 1 mm horizontal or downsloping ST-segment depression 80 milliseconds after the J point or more than 1 mm of additional ST-segment rise in leads without pathologic Q waves. After achieving peak workload, the treadmill stopped (no "cool-down" period was allowed) and the patients immediately laid on a bed, situated next to the treadmill. The patients remained in the supine position for 5 minutes, which was considered the recovery period (this period was prolonged in case the symptoms or electrocardiographic changes were persistent). The reduction in the heart rate from its value at peak exercise to the rate 1 minute later was determined as heart rate recovery.

Standard single-isotope (technetium-99m–tetrofosmin) MPI testing at rest and during stress was performed on all patients. Single-photon emission computed tomographic images using a dual-headed large field-of-view rotating camera with a high-resolution parallel-hole collimator were obtained.

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric.

3. Results:

Table 1		**Non diabetics**	**Diabetics**	**Chi-square test**	
		No. = 50	**No. = 50**	**X^2/t***	**P-value**
Sex	Female	14 (28.0%)	11 (22.0%)	0.480	0.488
	Male	36 (72.0%)	39 (78.0%)		
Age	Mean ± SD	51.44 ± 8.76	58.94 ± 7.89	4.497*	0.000
	Range	27 – 68	43 – 84		
HTN	Negative	25 (50.0%)	14 (28.0%)	5.086	0.024
	Positive	25 (50.0%)	36 (72.0%)		
Dyslipidemia	Negative	35 (70.0%)	32 (64.0%)	0.407	0.523
	Positive	15 (30.0%)	18 (36.0%)		
Smoking	Non smoker	33 (66.0%)	32 (64.0%)	0.890	0.641
	Smoker	12 (24.0%)	10 (20.0%)		
	Ex smoker	5 (10.0%)	8 (16.0%)		
Chest pain	Negative	17 (34.0%)	22 (44.0%)	1.051	0.305
	Positive	33 (66.0%)	28 (56.0%)		
Resting ECG	Abnormal	18 (36.0%)	23 (46.0%)	1.033	0.309
	Normal	32 (64.0%)	27 (54.0%)		

This study included 100 patients (50 diabetic and 50 non diabetic) their ages ranged from 27 to 82 years with a mean of 55±9. The study population included 75 males and 25 females.

We considered heart rate recovery to be abnormal when it was 19 bpm or less than that. 31 patients had an abnormal heart rate recovery 14 of them (28%) were non diabetics and 17 patients (34%) were diabetics.

As regard presence of diabetes, patients with diabetes tends to be of older age, men, hypertensive and dyslipidemic. The main characteristics of the patients according to presence or absence of diabetes are presented in table 1.

Resting heart rate, resting and peak systolic blood pressure were higher in the diabetic group than the non diabetic group but peak heart rate was higher in the non diabetic group with high statistically significant difference (138± 14 vs 146± 16 p=0.009).

Patients in the non diabetic group tend to exercise for longer period and tend to had more ST segment changes during exercise.

Patients with abnormalities in the SPECT MPI were higher in the diabetic group with statistically significant difference between the diabetic group and the non diabetic group (30 patients [60%] vs 19[38%] p=0.028).

Table 2		**Non diabetics**	**Diabetics**	**Independent t-test**	
		No. = 50	**No. = 50**	**t**	**P-value**
Resting SBP	Mean ± SD	130.20 ± 18.35	131.60 ± 14.90	0.419	0.676
	Range	90 – 170	110 – 170		
Resting DBP	Mean ± SD	83.00 ± 9.53	82.80 ± 6.71	-0.121	0.904
	Range	60 – 100	70 – 110		
Peak SBP	Mean ± SD	156.20 ± 25.55	168.40 ± 32.09	2.103	0.038
	Range	110 – 240	100 – 260		
Duration of exercise	Mean ± SD	7.50 ± 1.86	6.33 ± 1.75	-3.225	0.002
Exercise ECG changes	Negative	37 (74.0%)	42 (84.0%)	1.507	0.220
	Positive	13 (26.0%)	8 (16.0%)		
SPECT	Negative	31 (62.0%)	20 (40.0%)	4.842	0.028
	Positive	19 (38.0%)	30 (60.0%)		

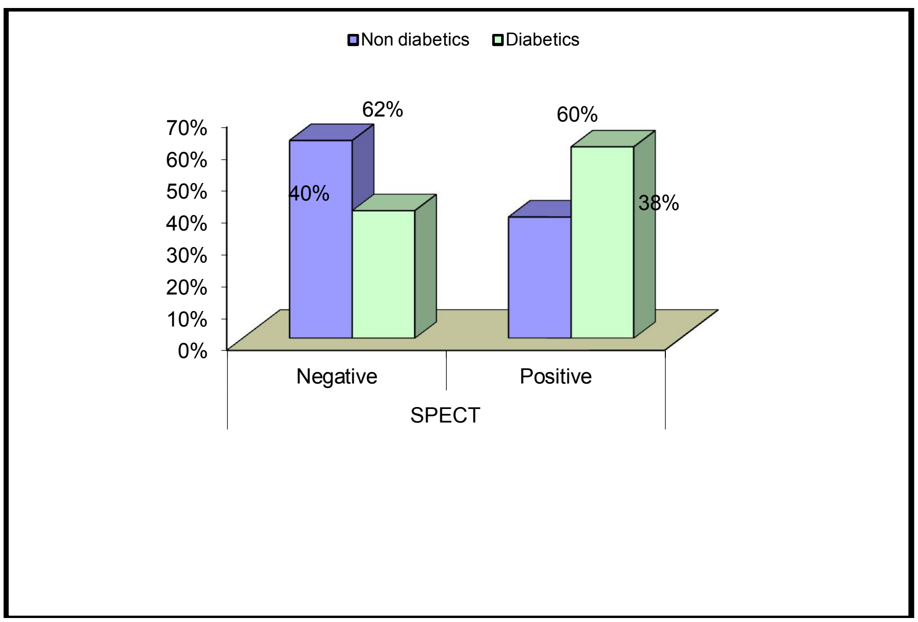
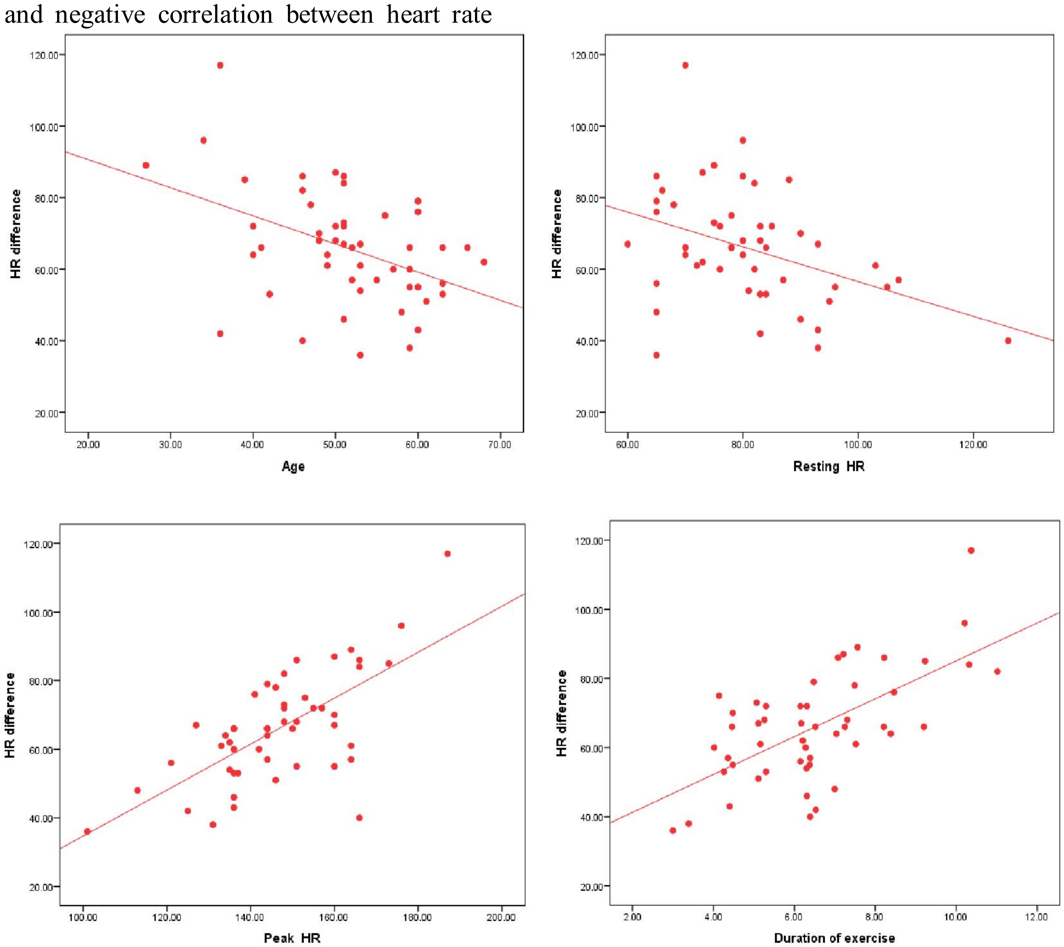


Fig 1

In the non diabetic group: patients with abnormal heart rate recovery tend to be of an older age, males, hypertensive and dyslipidemic. clinical characteristics of the non diabetic patients in table 3.

Table 3		HRR < 19	HRR > 19	Chi-square test	
		No. = 14	No. = 36	X²/t*	P-value
Sex	Female	1 (7.1%)	13 (36.1%)	4.196	0.041
	Male	13 (92.9%)	23 (63.9%)		
Age	Mean ± SD	55.57 ± 5.87	49.83 ± 9.23	-2.155*	0.036
	Range	42 – 63	27 – 68		
HTN	Negative	4 (28.6%)	21 (58.3%)	3.571	0.059
	Positive	10 (71.4%)	15 (41.7%)		
Dyslipidemia	Negative	8 (57.1%)	27 (75.0%)	1.531	0.216
	Positive	6 (42.9%)	9 (25.0%)		
Smoking	Non smoker	10 (71.4%)	23 (63.9%	0.299	0.861
	Smoker	3 (21.4%)	9 (25.0%)		
	Ex smoker	1 (7.1%)	4 (11.1%)		
Chest pain	Negative	4 (28.6%)	13 (36.1%)	0.255	0.613
	Positive	10 (71.4%)	23 (63.9%)		
	Positive	6 (42.9%)	13 (36.1%)		
Resting ECG	Abnormal	6 (42.9%)	12 (33.3%)	0.397	0.529
	Normal	8 (57.1%)	24 (66.7%)		

There was positive correlation between heart rate recovery and peak heart rate and also with duration of exercise and negative correlation between heart rate recovery and age and also with resting heart rate (fig 2).

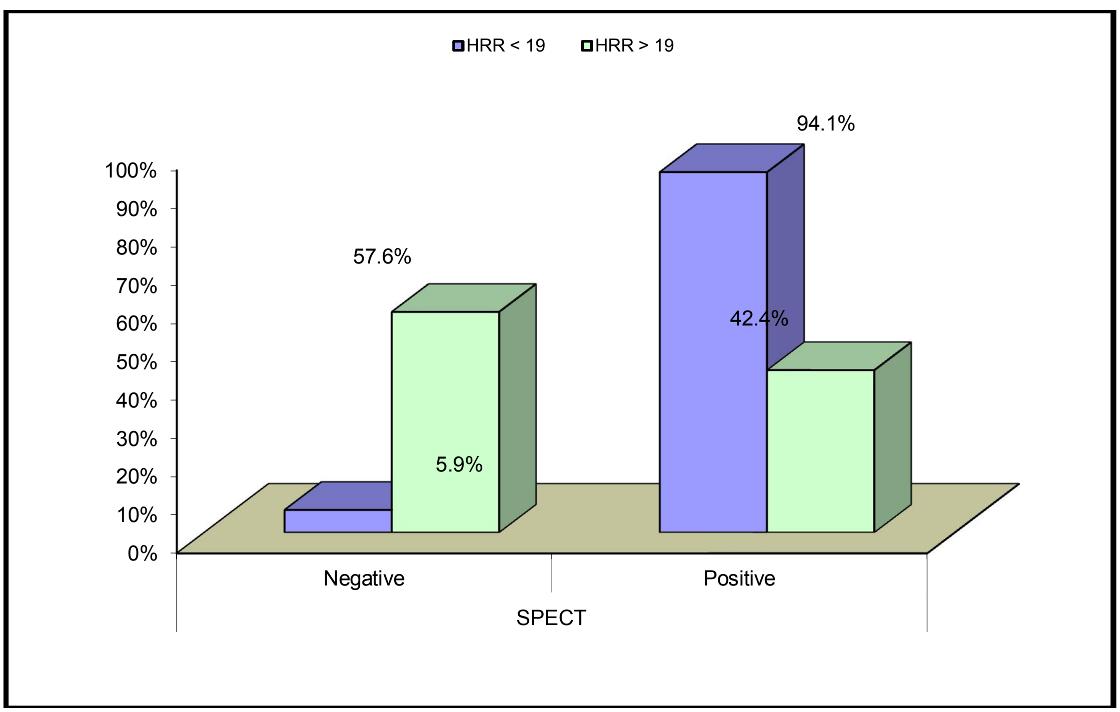


In the diabetic group: patients with abnormal heart rate recovery tend to be of an older age, males, hypertensive, dyslipidemic and had abnormal resting ECG.

Clinical characteristics in the diabetic group in table 4.

Table 4		**HRR < 19**	**HRR > 19**	**Chi-square test**	
		No. = 17	**No. = 30**	**X²/t***	**P-value**
Sex	Female	3 (17.6%)	8 (24.2%)	0.284	0.594
	Male	14 (82.4%)	25 (75.8%)		
Age	Mean ± SD	59.47 ± 6.68	58.67 ± 8.53	-0.338*	0.737
	Range	47 – 73	43 – 84		
HTN	Negative	4 (23.5%)	10 (30.3%)	0.255	0.613
	Positive	13 (76.5%)	23 (69.7%)		
Dyslipidemia	Negative	11 (64.7%)	21 (63.6%)	0.006	0.941
	Positive	6 (35.3%)	12 (36.4%)		
Smoking	Non smoker	10 (58.8%)	22 (66.7%)	1.092	0.579
	Smoker	3 (17.6%)	7 (21.2%)		
	Ex smoker	4 (23.5%)	4 (12.1%)		
Chest pain	Negative	7 (41.2%)	15 (45.5%)	0.083	0.773
	Positive	10 (58.8%)	18 (54.5%)		
Resting ECG	Abnormal	13 (76.5%)	10 (30.3%)	9.628	0.002
	Normal	4 (23.5%)	23 (69.7%)		

16 patients (94.1%) with abnormal heart rate recovery had abnormal results in SPECT MPI. (fig5)



There is positive correlation between heart rate recovery and peak heart rate, duration of exercise and mean percentage of ejection fraction, and there is negative correlation between heart rate recovery and resting heart rate.(fig 3)

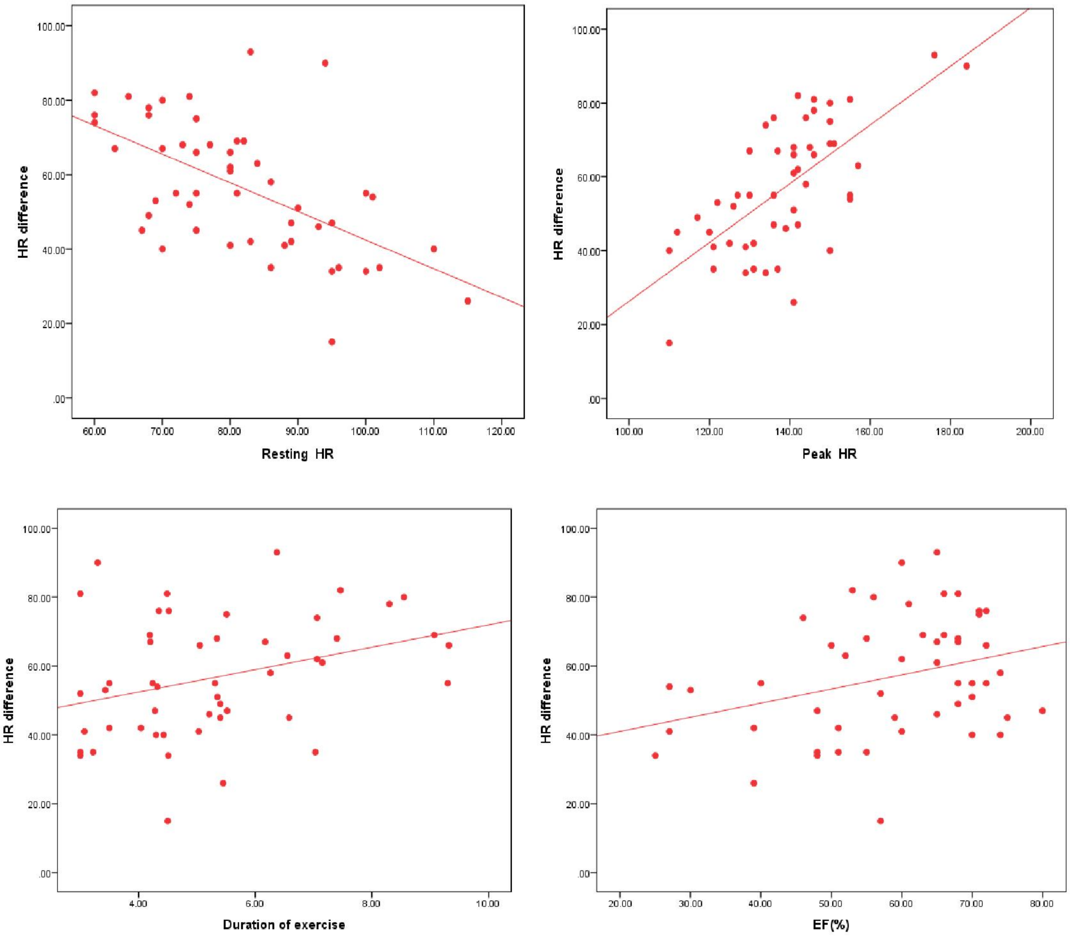


Fig 3

4. Discussion:

A number of reports have studied the pathophysiology of the increase in heart rate during exercise testing and of its decrease at the termination of the test which are due to change in tone balances between the sympathetic and the parasympathetic nervous system **(Imai et al 2004).**

The principal findings of this study are as follows:(1) Exercise heart rate responses are more frequently impaired in patients with vs without diabetes, and (2) abnormal heart rate recovery is associated with abnormality in SPECT imaging in patients both with and without diabetes.

Delayed decrease in the heart rate during the first minute after treadmill testing appears to be an important predictor of all cause mortality independent of the workload, the presence or absence of myocardial perfusion defects and the change in heart rate during exercise **(Cole et al 2000, Watanabe et al 2001).**

In the period between September 1990 and December 1993, 2428 patients were referred for symptom-limited exercise test and single-photon-emission computed tomography with thallium scintigraphy at the Cleveland clinic for evaluation of known or suspected coronary artery disease. heart rate recovery was defined as the difference in heart rate at peak exercise and that measured 1 minute later, all subjects underwent a 2 minutes cool-down period during recovery for two minutes before stopping exercise. Patients with an abnormal heart rate recovery <_12 bpm were at markedly increased risk of death compared to those with a normal heart rate recovery **(Cole et al 1999),** diabetic patients were included like our study.

Left ventricular systolic dysfunction is one of the most powerful predictors of risk in patients with known or suspected coronary disease **watanabe et al** studied this issue in 5438 patients referred for exercise stress echocardiography at the Cleveland Clinic between October 1990 and April 1999, Patients were excluded if they were<_30 years of age, had a history of heart failure, valvular or congenital heart disease, had an implanted pacemaker or atrial fibrillation, or used digoxin.

Heart rate recovery was defined as the difference in heart rate between peak exercise and 1 minute later; a value of <_18 beats per minute was considered abnormal. Patients assumed the left lateral decubitus position after exercise and its conclusion was that Even in the absence of a cool-down period and even after accounting for left ventricular systolic function, heart rate recovery was predictive of death independent of and in addition to left ventricular systolic dysfunction **(Watanabe et al 2001).**

Myocardial SPECT imaging is a reliable method for assessing myocardial perfusion **Gera et al** found that abnormal HRR on exercise treadmill testing was associated with a high prevalence of abnormal and high-risk stress MPI findings, even in patients without other exercise treadmill testing findings that traditionally would prompt further testing. These findings suggest that further testing with stress MPI should be considered in patients with abnormal HRR on routine exercise treadmill testing. HRR at 1 minute was defined as the difference between heart rate at 1 minute after cessation of peak exercise (at the end of the cool-down period) and maximal heart rate achieved during exercise. This study was done in only men **(Gera et al 2008).**

Attenuated heart rate recovery (HRR) following maximal exercise test is a predictor of mortality in healthy adults and in those referred for diagnostic testing **(cole et al 1999).** These findings are independent of workload achieved during the test, presence or absence of myocardial perfusion defects, and changes in heart rate during the exercise test. Panzer et al **(Panzer et al 2008)** reported that fasting plasma glucose is strongly and independently associated with abnormal HRR, even at non-diabetic levels. Similarly, data from the Framingham Heart Study have shown reduced heart rate variability and sympathetic- parasympathetic imbalance in adults with diabetes and impaired fasting glucose **(Ma¨kimattila S et al 2000, - Singh JP et al 2000).** The predictive effect of low HRR on outcome might be especially pronounced in patients with diabetes because of the known association of diabetes with autonomic dysfunction **(Giacca A et al 1998).**

Chacko et al has found that HRR provides information beyond traditional CV risk factors that could aid in the clinical risk stratification of patients with T2DM. The results suggest that HRR results should be incorporated into standard diagnostic treadmill testing reports and target those patients with T2DM and attenuated HRR who can benefit from directed therapies. Exercise testing was performed at a single site, using a modified Bruce protocol. The recovery period consisted of 2 min of walking at 1.9 km (1.2 miles) per hour on a 0% grade.

In the look AHEAD study (action for health in diabetes) study, 5783 obese/overweight patients aged 45-76 years undergo symptom limited exercise testing, cut of value for heart rate recovery was less than 22 BPM two minutes after peak exercise. The most frequent abnormality was impaired exercise capacity (12.0%), followed by ST segment depression (7.6%), heart rate recovery abnormalities (5.0%), exercise-induced angina (1.1%), and ventricular arrhythmias (0.7%).

In our study there were two divisions, the first whether the patient is diabetic or non diabetic and the second according to heart rate recovery 1 minute after peak exercise and the cut of value was 19 beats per minutes.

5. Conclusion:

In conclusion, myocardial ischemia, as it is mainly assessed via myocardial perfusion scintigraphy, has a considerable effect on the heart-rate recovery value. It seems that the heart-rate recovery value 1 min after exercise is indicative as a marker of the severity of myocardial ischemia. More studies, with well defined conditions for the calculation of its value, are required for the definition of a generally accepted lowest normal value.

In an era in which a continuous effort is taking place for deriving as many elements as possible from inexpensive and safe examinations, the calculation of the heart rate recovery value during exercise testing will maximize not only the prognostic value of the study, but also the information it provides for the assessment of the severity of myocardial ischemia. Finally, it may contribute to the selection of the patients who are in need of more expensive and complicated examination methods, such as the myocardial perfusion scintigram. As an additional criterion, the incremental value of heart-rate recovery, required to improve the decision making process, needs further investigation.

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