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ORIGINAL ARTICLE

Determinants and Prognostic Value of Heart Rate Recovery in Short-Term Outcome of Percutaneous Coronary Intervention in Patients with and Without Type 2 Diabetes

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ABSTRCT

Background: Heart rate recovery (HRR) after exercise is an independent prognostic tool for cardiovascular (CV) morbidity and mortality. The aim of this study is to detect the determinants of HRR in ischemic heart disease patients undergoing PCI with and without Type II Diabetes (T2D) and to assess its short term prognostic value.

Methods: We examined the correlation between HRR and Clinical, Laboratory, Echocardiography, stress test and coronary angiography data in our cohort (100 patients with positive exercise test and PCI within 90 days, age 49 ±10 years, 71 males, 50% with T2D). We followed them up for 6 months and tested how impaired HRR (IHRR) predicts CV morbidity and mortality and compared data between diabetics and non-diabetics.

Results: HRR closely correlated with age, presence of T2D, resting HR, METs, Diastolic dysfunction, LA size and number of coronary lesions. A stepwise linear regression model revealed age, T2D, Resting HR and Diastolic dysfunction as predictors of IHRR. In diabetics HRR was strongly correlated with resting HR, METs, LA size and TG level. A stepwise linear regression model showed resting HR, LA size and TG level as predictors of IHRR. In non diabetics only resting HR was strongly correlated with HRR. Kaplan-Meier survival analysis showed IHRR predicted mortality. Cox regression models found that IHRR predicted arrhythmia and CV composite end point. In diabetics IHRR predicted CV composite end point but not in non diabetics.

Conclusions: Age, T2D, Resting HR, and Diastolic dysfunction were determinants of HRR among PCI patients. In diabetics resting HR, LA size and TG level its determinants. In non diabetics resting HR was the only determinant. In patients with T2D IHRR predicted CV composite end point but did not predict mortality. In non diabetics IHRR did not predict any of the endpoints.

Keyworsd: Heart rate recovery; exercise stress test; type two diabetes; percutaneous coronary intervention

INTRODUCTION

Heart rate recovery (HRR) is measured easily in the recovery phase of treadmill exercise testing and used to determine depression in the parasympathetic tone so it can be used to evaluate the basal autonomic balance in cardiovascular (CV) diseases specially in coronary artery disease (CAD) patients [1,2].It is defined as the difference between heart rate (HR) achieved at peak exercise and after a certain period in the recovery phase. One minute HRR has a robust data in literature and was found to be optimal predictor of CV events [3].Impaired HRR (IHRR) definition in most of previous studies was ≤8 to 21 beats though ≤12 beats was the most commonly used definition and it was consistently correlated with cardiovascular events and is more common among ischemic heart disease patients with Type II diabetes than in those without and is a powerful indicator of cardiovascular autonomic imbalance, which is a complication of diabetes and is a strong predictor of increased mortality [4, 5]. It is well established that larger declines in heart rate after exercise predict lower mortality [6] and its impairment is a good predictor of both morbidity and mortality in healthy people [8], Diabetics [4, 10, 11], heart failure [12, 13] and CAD patients [14], however, its prognostic value in patients undergoing

Percutaneous coronary intervention is not as well studied [9].The aim of this study is to examine the Determinants and Prognostic Value of Heart rate Recovery in Short-term outcome of PCI in Patients with ischemic heart disease with and without Type II Diabetes mellitus.

METHODS

This study was conducted at Zagazig University Hospital from January 2016 to March 2019 and it was a prospective cross sectional study. The cohort was derived from those patients who underwent symptom-limited exercise treadmill tests according to Bruce Protocol with a goal of achieving ≥ 85% of maximum predicted HR. Exercise test was followed by an active cool down period of 2 minutes of walking. We examined 178 consecutive patients with positive exercise stress test who underwent coronary angiography +/- PCI within 90 days. 117 patients were having a significant lesion(s) that required intervention. 8 patients showed multivessel disease that required surgery sent for CABG so excluded from the study. Another 5 patients had left main coronary artery disease sent for CABG and also excluded from the study. 4 patients were missed during the follow up so also excluded from the study. Informed consent was taken from all patients to be included in the study. Our cohort (100 patients) was followed up for 6 months after PCI and was divided into four groups as follow:-

Patients with T2DM and having normal HRR (26 patients).

Patients with T2DM and having impaired HRR (24 patients).

Non diabetic patients and having normal HRR (39 patients).

Non diabetic patients and having impaired HRR (11 patients).

All groups were matched in HR at rest and at peak exercise, HRR, clinical characteristics, lab characteristics, echocardiography characteristics, number and severity of coronary lesions, Primary end point (Cardiovascular mortality), Secondary end points (Acute coronary syndrome (ACS), Instent restenosis, Instent thrombosis, Repeated PCI or CABG, Stroke, Heart failure and arrhythmias) and CV composite end point of death and all secondary end points. HRR was defined as the difference in heart rate from maximum exercise to one minute in recovery period after exercise. A positive exercise test was defined by the development of ST-segment horizontal or down sloping depression (≥1.0 mm at 80 ms after the J point) in two or more contiguous leads during exercise or in the recovery phase. A complete revascularization was defined as the PCI procedure in which all diseased arterial system with vessel size ≥2 mm and at least one significant stenosis≥70 % received a stent in any epicardial coronary vessel or more than 50% in case of left main coronary artery. The procedure of PCI was considered successful if it achieved a final thrombolysis in myocardial infarction (TIMI) flow grade 3 and leaving no more than 30% stenosis of the intervened upon epicardial coronary vessels and without occurrence of complications. Diabetes mellitus was defined by the ADA 2013 criteria (HbA1C ≥6.5% or FPG ≥126 mg/dl or 2-h plasma glucose ≥200 mg/dl) or if the patient has a history of diabetes and still on medical treatment. Hypertension was defined by the criteria of the 2013 ESH/ESC Guidelines. Persons were considered hypertensive if 2 or more blood pressure readings were greater than or equal to 140 mm Hg systolic and/or 90 mm Hg diastolic or if the patient is already diagnosed as hypertensive and on regular antihypertensive drugs to control his blood pressure. Dyslipidemia was defined according to the ATP III definition as one or more of the following: total cholesterol more than 200 mg/dL, low density lipoprotein cholesterol (LDL) more than 130 mg/dL, high-density lipoprotein-cholesterol (HDL) ≤ 40 mg/dL in males and ≤ 50 mg/dL in females and triglycerides more than 150 mg/dL or the use of anti dyslipidemia drugs. Acute coronary syndrome (ACS) was defined as the occurrence of unstable angina, non ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI).

Inclusion criteria:

All patients with positive exercise treadmill stress test who underwent a coronary angiography and a complete successful revascularization by PCI within 90 days from the exercise test were included in the study.

Exclusion criteria:

Patients with heart failure or heart failure history, severe valvular heart disease, congenital heart disease, end-stage renal failure needing dialysis, any other medical condition that can affect survival, patients who refused to be followed up at any time during the study and patients who underwent CABG operation.

Full medical history was taken from all patients including the demographic data (age, gender, place of residence) and CAD risk factors. All patients were subjected to detailed clinical examination, 12 lead surface ECG, Plain chest x-ray, detailed transthoracic echocardiogram which was performed to all patients using a GE Vivid 7 ultrasound system equipped with 2.5 MHz probe, laboratory investigations (Fasting blood sugar, Complete blood count, Lipid profile, Liver functions; SGPT & SGOT, Kidney functions; blood urea and serum creatinine level).

All patients were prescribed post PCI standard medical treatment including the dual antiplatelet therapy, statin and other medications as indicated by concomitant medical conditions and were followed up in the clinic 1, 3 and 6 months after PCI. In addition they were instructed to contact the clinic for any symptoms at any stage during follow up period. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving human.

STATISTICAL ANALYSIS

All data was tabulated, statistically analyzed and groups were matched using IBM SPSS Statistics 25 for Windows software. Normally distributed continuous variables were reported as mean ± SD. Categorical variables were reported as proportions and compared using the Chi Square test. Continuous variables were compared using the t-test. A probability value of < 0.05 was considered statistically significant.All available variables were included in a univariate analysis and all factors that were significantly correlated with HRR were entered into a stepwise linear regression model to determine the predictors of impaired HRR in whole study population and in subgroups.We also used Cox regression models to calculate hazard ratios (HRs) for each end point alone and for the composite end point with adjustment for all covariates. Then we compared the data between diabetics and non diabetics and between those with IHRR and those with normal HRR (NHRR). Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut off point of HRR to predict the CV composite end point of death and all secondary end points with the highest combination of sensitivity and specificity.

RESULTS

Among 100 patients who were finally included in the current study, there were 29 (29%) women with a mean (±SD) age of 49.79±9.63 and 71 (71%) men with a mean age of 48.66 ±8.9. The overall mean age (±SD) was 48.99 ±15.08. The patients' demographics, clinical data, coronary angiography data and their outcomes after PCI and are listed in table 1. HRR had the closest univariate correlation with age(r= -0.22; P=0.029), presence of DM (r= -0.21; P=0.032), resting HR(r= -0.67; p<0.001),METs achieved during exercise test(r= 0.32 p=0.001), Diastolic dysfunction (r=-0.27; p=0.006), LA size(r=-0.34; p=0.001), number of significant coronary artery lesions during angiography(r=-0.25;p=0.013). When all factors entered into a stepwise linear regression model(R=0.55, p<0.0001) age (p= 0.017), presence of T2D (p=0.042), Resting HR (p<0.0001) and Diastolic dysfunction (p=0.036) were the predictors of IHRR in our cohort. In the diabetics HRR had the strongest univariate correlation (Figure 1) with resting HR (r= -0.78; p<0.001), METs achieved during exercise (r= 0.45 p=0.001), LA size(r=-0.39; p=0.005) and TG level (r=-0.38; p=0.006). A stepwise linear regression model (R=0.503, p=0.002) showed that Resting HR (p<0.0001), LA size (p=0.0015) and TG level (p=0.0376) as the only predictors of IHRR. A Comparison in Echocardiography data between Diabetics and non diabetics is shown in table 4-A and between impaired and normal HRR groups in table 4-B. In non diabetics, the only variable that was significantly correlated with HRR was resting HR (r= 0.55 p; p<0.001) (figure 2).From our study receiver operating characteristic (ROC) curve analysis a value of HRR≤15 beats was found to be a the best cut off point as a predictor of the CV composite end point with the highest combination of sensitivity and specificity (Figure 3).A Comparison in demographics, clinical, stress test, coronary angiography and intervention data and clinical outcomes between Diabetics and non diabetics is presented in table 2 and between patients with impaired HRR and those with normal HRR groups is presented in table 3.During the six months of follow-up period, 14 patients (14%) reached a composite end point, including 3 patients (3%) with cardiovascular death, 8 (8%) with acute coronary events, 5 (5%) with repeated PCI, 1 (1%) with instent restenosis, 5 (5%) with arrhythmia, 5 (5%) with heart failure and 1 (1%) with stroke.Of 35 patients with IHRR, 9 patients (25.7%) reached a CV composite endpoint of death, ACS, repeated PCI, significant arrhythmia, heart failure and stroke versus 5 patients (7.6%) of those with a NHRR had cardiac events. Kaplan-Meier survival analysis showed that IHRR did predict mortality at 6 months of follow up as shown in Figure 4- A (Log rank 5.7372; P = 0.0166) but no significant difference (Logrank 0.3401; P = 0.5598) was found between diabetics and non diabetics (Fig. 4-B). Cox regression models to calculate hazard ratios (HRs) for each end point alone and the composite end point with adjustment for covariates found that IHRR did predict arrhythmia (HR 1.68 [95% CI [1.22–1.99], P = 0.0274) and both CV composite end point at 6 months (HR 1.23 [95% CI [1.16–1.45], P = 0.0092). In diabetics IHRR did predict a CV composite end point at 6 months of follow up (HR 1.44 [95% CI [1.33–1.60], P = 0.0005) but not in non-diabetics.

Table 1: Demographics and main characteristics of the study population. Values are the mean +/- SD or n (%).

Clinical variable	Mean +/- SD or n (%).
Age	48.99 ±15.08
Gender	71 / 29 (71/ 29%)
Risk factors for CAD	
Diabetes mellitus	50 (50%)
Hypertension	43 (43%)
Dyslipedemia	45 (45%)
Smoking	67 (67%)
PVD	5 (5%)
Positive FH for premature CAD	19 (19%)
No of risk factors	2.56 ± 1.38
Stress test data	
Resting HR (bpm)	75.57 ± 19.40
Peak exercise HR (bpm)	149.34 ± 21.96
HR 1 min in recovery (bpm)	126.62 ± 20.4
HRR (beats)	22.72 ± 14.13
METs Achieved	8.97 ± 3.74
Populatin with Impaired HRR	35 (35%)
Coronary angiography data	
NO OF LESION IN ANGIO	1.70 ±.96
LM Lesion	8 (4.7%)
LAD Lesion	62 (36.4%)
LCX Lesion	21 (12.3%)
RCA Lesion	38 (22.4%)
Ramus Intermedius	5 (2.9%)
Stents inserted	1.59 ±.8
Primary end point (CV mortality)	3(3%)
Secondary end points	11(11%)
CV composite end point	14(14%)

Table 2: Comparison in demographics, clinical, Stress test, coronary angiography and intervention data and clinical outcomes between Diabetics and non-diabetics. Values are the mean +/- SD or n (%).

Clinical variable	PCI group with DM	PCI group without DM (n=50)	P value
Age	49.12± 15.29	48.86±16.89	0.8870
Gender(M/F)	33/17	38/12	0.2729
Risk factors for CAD			

Clinical variable	PCI group with DM	PCI group without DM (n=50)	P value
Hypertension	29 (58%)	14 (28%)	**0.0026**
Dyslipedemia	30 (60%)	15 (30%)	**0.0027**
Smoking	32(64%)	35(70%)	0.5256
PVD	5(10%)	0	**0.0225**
Positive FH for premature CAD	8(16%)	11(22%)	0.4467
No of risk factors	3.08± 1.2	1.5±0.99	0.0001
Stress test data			
Resting HR (bpm)	75.62±20.82	75.52±13.9	0.9681
Peak exercise HR (bpm)	149.54±21.5	149.24±20.11	0.9055
HR 1 min in recovery (bpm)	128.84±22.9	124±18.61	0.0937
HRR (beats)	20.7±15.32	24.84±13.69	**0.0324**
METs Achieved	8.39±2.79	9.55±3.08	**0.0006**
Populatin with Impaired HRR	24 (48%)	11(22%)	**0.0067**
Coronary angiography data			
NO OF LESION IN ANGIO	73(54.5%)	61(45.5 %)	0.1891
Mean no of coronary lesion	1.98 ±0.99	1.42± 0.84	**0.0029**
LM Lesion	6	2	0.1424
LAD Lesion	29	33	0.4122
LCX Lesion	13	8	0.2219
RCA Lesion	22	16	0.2187
Ramus Intermedius	3	2	0.6480
Stents inserted	1.84±0.91	1.34±0.59	0.0015
End points			
Primary end point (CV mortality)	2(4%)	1(2%)	0.5597
Secondary end points	7(14%)	4(8%)	0.3401
CV composite end point	9(18%)	5(10%)	0.2514

Table 3: Comparisons in demographics, clinical, stress test and coronary angiography data and their outcomes after PCI between the impaired HRR and the Normal HRR groups. Values are the mean +/- SD or n (%).

Clinical variable	PCI group with impaired HRR (≤15) (n=35)	PCI group with normal HRR (›15) (n=65)	P value
Age	51.08± 14.73	47.86± 17 .13	0.0908
Gender(M/F)	24/11	47/18	0.6960
Risk factors for CAD			
DM	24(68.6%)	26(40%)	**0.0067**
Hypertension	17(48.6)	26(40%)	0.4113
Dyslipedemia	14(40%)	31(47%)	0.4631

Clinical variable	PCI group with impaired HRR (≤15) (n=35)	PCI group with normal HRR (›15) (n=65)	P value
Smoking	21(60%)	46(70.8%)	0.2771
PVD	3 (8.6%)	2 (3.1%)	0.2315
Positive FH for CAD	7 (20%)	12(18.5%)	0.8524
No of risk factors	2.46±1.52	2.2±1.29	0.3690
Stress test data			
Resting HR (bpm)	86.34±18.5	69.77±21.6	**0.0001**
Peak exercise HR (bpm)	149.17±19.5	149.51±17.47	0.8913
HR 1 min in recovery (bpm)	137.11±15.56	120.97± 13.81	**0.0001**
HRR (beats)	12.06±2.94	28.53±6.87	**0.0001**
METs Achieved	8.05±1.00	9.47±1.85	**0.0001**
Coronary angiography data			
NO of coronary lesions	1.97±1.1	1.55±0.85	**0.0364**
LM Lesion	4 (11.4)	4 (6.1%)	0.3562
LAD Lesion	23 (65.7%)	39 (60%)	0.5764
LCX Lesion	10 (28.6%)	11 (16.9%)	0.1747
RCA Lesion	10 (28.6%)	28(43%)	0.1561
Ramus Intermedius	3 (8.6%)	2(3.1%)	0.2315
Stents inserted	1.83±0.98	1.46±0.66	**0.0270**
Primary end point (CV Mortality)	3 (8.6%)	0	**0.0171**
Secondary end points	6 (17.1%)	5 (7.6%)	**0.1484**
CV composite end point	9 (25.7%)	5(7.6%)	**0.0137**

Table 4: Comparison in Echocardiography data between Diabetics and non diabetics (A) and between the impaired and normal HRR groups (B). Values are the mean +/- SD or n (%).

A Echocardiography parameters	**PCI group with DM (n=50)**	**PCI group without DM (n=50)**	**P value**
LVEDD (cm)	4.90 ±1.55	4.95±0.97	0.6563
LVESD (cm)	3.26±1.46	3.26±0.91	1.0000
EF %	61.26±7.98	63.06±5.51	0.1924
RWMA	6 (12%)	7 (14%)	0.7673
SWT (cm)	1.13±0.32	0.96±0.28	0.2963
PWT (cm)	1.02±0.29	0.95±0.30	0.0143
LA	3.71±1.21	3.22±0.98	**0.0001**
Diastolic dysfunction	32 (64%)	14 (28%)	**0.0003**
B Echocardiography parameters	**PCI group with impaired HRR** (n=35)	**PCI group with normal HRR** (n=65)	**P value**

A Echocardiography parameters	PCI group with DM (n=50)	PCI group without DM (n=50)	P value
LVEDD (cm)	4.92±1.56	4.93±1.28	0.9833
LVESD (cm)	3.24±1.1	3.27±1.12	0.7457
EF %	62.46±6.74	62.00±7.01	0.7457
RWMA	3(8.6%)	10(15.3%)	0.3363
SWT (cm)	1.12±0.33	1.01±0.29	0.0349
PWT (cm)	1.02±0.33	0.97±0.21	0.1070
LA (cm)	3.74±0.94	3.31±0.86	**0.0009**
Diastolic dysfunction	23(65.7%)	23(35.4%)	**0.0039**

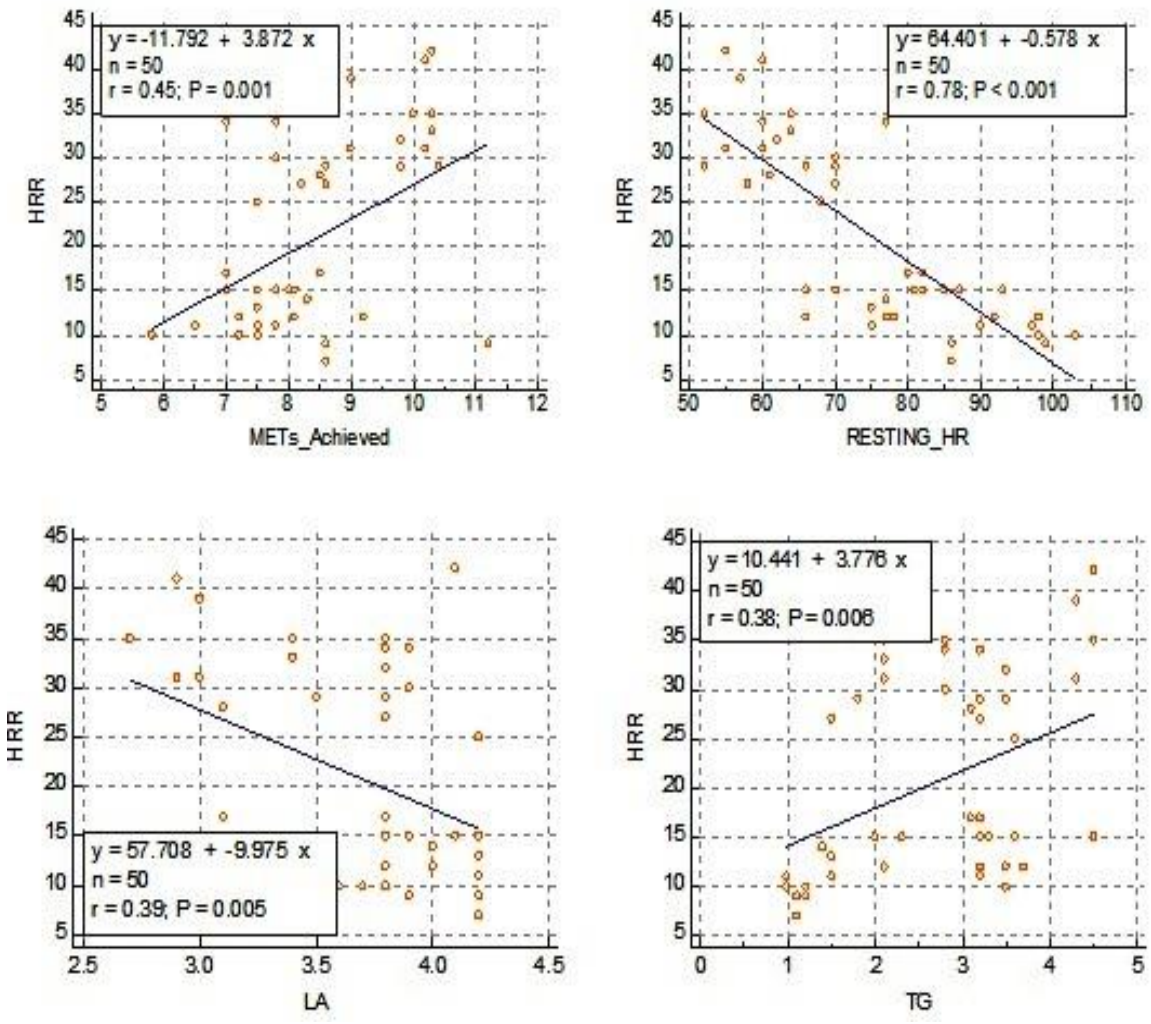

Fig 1: Significant correlations among the diabetic subgroup between heart rate recovery after one minute in recovery stage and Resting HR, METs achieved during exercise stress testing, LA size and TG level

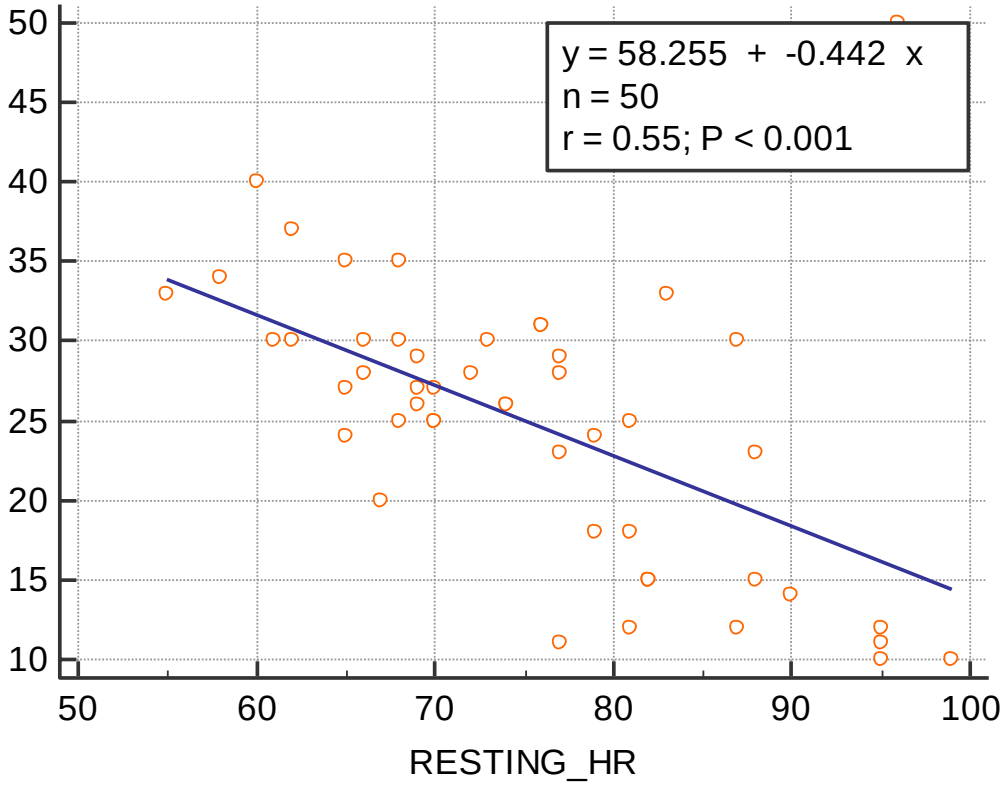

Fig. 2 Significant correlation between heart rate recovery after one minute in recovery stage and Resting HR among the Non diabetic subgroup**.**

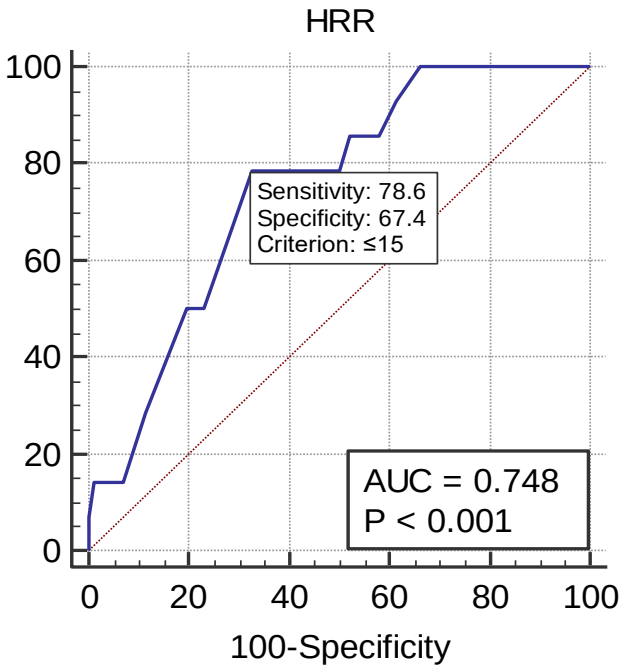

Figure 3: ROC curve for the whole study population

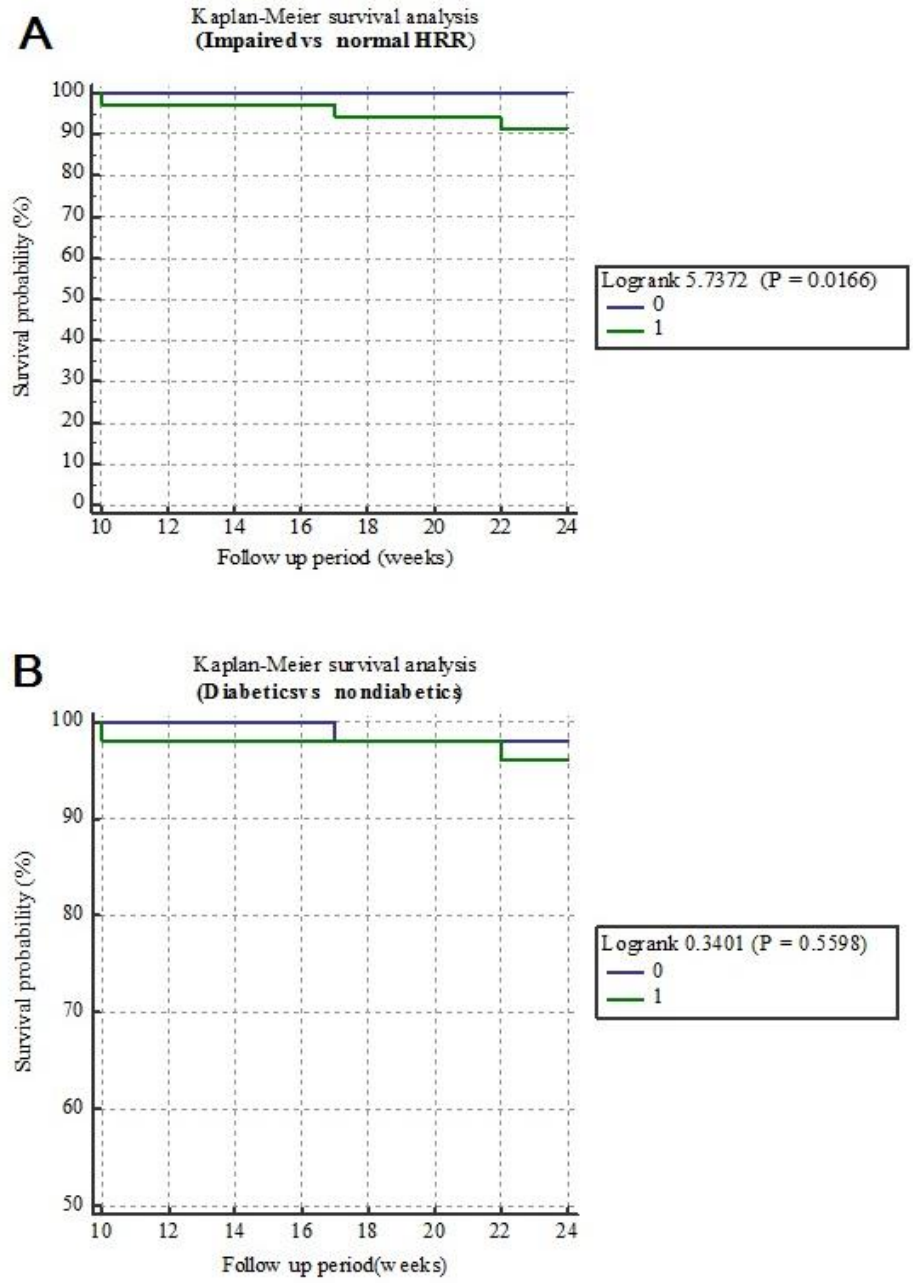

Fig.4: Kaplan Miere survival curve for the impaired versus normal HRR groups (A). Green represents the PCI patients with impaired HRR and blue represents the PCI patients with normal HRR; (Log rank 5.7372; P = 0.0166). and Kaplan Miere survival curve for diabetics versus non diabetics (B). Blue represents the PCI patients without type 2 DM and Green represents the PCI patients with type 2DM; Log rank 0.3401 (P = 0.5598).

DISCUSSION

In normal population vagal reactivitation is the main factor that influences the recovery of heart rate to its pre-exercise level in the early (during the 1st minute) post exercise phase while sympathetic withdrawal is the main factor during the 2nd to 5th minute [2]. In patients with autonomic dysfunction, the autonomic balance that modulate the HR response is disturbed leading to an inability to slow down the HR directly after exercise; the so called impaired heart rate recovery [5, 15]. Previous studies in most of time have investigated the association between HRR as a parameter of autonomic function and a few associated determinants, whereas in our study we have examined at the same time many potential determinants. Moreover, we focused on studying the short term prognostic value of HRR in IHD patients who underwent PCI; whereas previous studies have mainly concentrating on the long term prognostic value [16]. Impaired HRR definition in previous studies was ≤8 - 25 [32] beats though ≤12 beats was the most commonly used definition [14, 27]. Watanabe et al. [12] used a cutoff point of 18 bpm and so did Ghaffari et al. [17] while Jouven et al. [32]found HRR <25 bpm is the best to predict

sudden cardiac death. Georgoulias et al. [19] defined it as less than 21 bpm. Also Kiviniemi et al. [20] and Karjalainen J. et al. [4]found a cut off value of 21 bpm a powerful predictor of a composite end point of CV death, acute coronary syndrome, stroke, and hospitalization for HF [4]. From our study receiver operating characteristic (ROC) curves analysis a value of HRR≤15 beats was found to be a the best cut off point as a predictor of the CV composite end point with the highest combination of sensitivity and specificity so was chosen as the optimal cut off point of HRR (Figure 3).

Determinants of heart rate recovery

In agreement with most of previous studies our study did find a strong correlation between the presence of T2D and impairment of HRR in patients with IHD undergoing PCI [4, 18].

Many of the previous studies found that IHRR is associated with higher level of HbA1c in diabetic patients [22], coronary aretery disease patients [23] as well as in general population [24]. Similarly we found a strong correlation between IHRR and higher levels of HbA1c in IHD patients undergoing PCI but in contrast to Karjalainen et al [4] and Singh et al. [24] we did not find such a significant association with fasting blood sugar levels among PCI patients with and without T2D.

In Healthy Individuals Antelmi et al. [25] reported faster HRR in women and younger subjects. In agreement with Lima et al. [26] we did find a significant association between older age and impairment of HRR but this finding was significant only among patients with but not without T2D.

In the current study we found a strong correlation between HRR and exercise capacity indicated by METs achieved during exercise test in both diabetics and non diabetics which was also found in previous studies [27, 28]. In contrast to Ghaffari et al. [17] who found a correlation between autonomic dysfunction and the degree of coronary occlusion severity at angiography, our results are matching with Karjalainen J.et al. [4] and Akyüz et al. [21] who did not find such a correlation between HRR and angiographic severity of coronary artery disease measured at time of PCI in both diabetics and non diabetics but we did find a strong correlation between number of coronary lesions and impairment of HRR. This could be explained by the larger size of ischemia burden indicated by number of lesions.Karjalainen et al. [4] found a weak correlation between autonomic dysfunction and diastolic dyfunction of the left ventricle. However we found this correlation a significant one. In contrast we did not find any relation between HRR and LV systolic function and these results are going with Nonaka et al. [29] and Ghaffari et al. [17]. As many of our patients were hypertensives (43%) and most of them had LVH we can explain the correlation between HRR and diastolic dysfunction due to the relative ischemia associating LVH. Among the other echocardiography parameters examined in the current study was the left atrial size which was found to be inversly correlated with HRR in patients with but not without T2D. This also could be explained by the relative ischemia that associates LVH especially with T2D as most of patients with LVH has diastolic dysfunction and LA enlargement.In agreement with 2 decades of epidemiologic data which have suggested a strong correlation between higher cardiovascular morbidity and mortality and higher resting heart rate [18] and in agreement with Saxena et al. [30] who reported that patients with CHD and high resting HR has increased total and CVD mortality, irrespective of the major coronary artery disease risk factors we also found a strong correlation between resting HRR and HRR. The higher the resting HR, the lower the HRR. Moreover, a previous study [30] showed that higher resting HR is linked to higher mortality and cardiovascular complications in patients with T2D and in the current study we found that resting heart rate was the only variable that is correlated with HRR among non diabetics. The higher the resting heart rate, the weaker the basal vagal tone which is well known to have a cardioprotective effect [31] so we can expect impairment of HRR in patients with higher resting HR as the early phase of recovery is dependant mainly on the reactivation of parasympathetic tone.

Prognostic value of heart rate recovery

In agreement with many studies [8, 9, 27] and a meta analysis done by Qiu et al [5] our Kaplan-Meier survival analysis (Fig 4- A) showed that impaired heart rate recovery did predict mortality. The difference is that we found this prediction at 6 months of follow up while the previous studies found this at a longer follow up periods. For decades autonomic dysfunction was consistently correlated with dysrhythmias and increased risk of sudden cardiac death. Jouven et al. [32] reported a significant relationship between sudden cardiac death including VT/VF as a cause of death and HRR on the long term follow up but in the current study we found that IHRR did predict the occurrence of VT/VF in the short term follow up period of 6 months which to the best of our knowledge is not reported before on the short term. Autonomic dysfunction especially parasympathetic abnormalities also have been demonstrated to play a role in the development of AF [33, 34]. In a study done by Maddox et al. [35] Patients with IHRR on exercise stress testing were found to be more likely to develop atrial fibrillation

when compared with those patients without IHRR. Actually we did not find such a relation. Mostly because of our small sample size in comparison to 8236 patients in Maddox et al. study [35]. Although the previously reported data about HRR and its prognostic value in diabetic patients [4, 32]in our diabetic subgroup IHRR did not predict mortality in Kaplan-Meier survival analysis or any individual end point at the short term of 6 months but did predict a CV composite end point. This could be due to the relatively small number of patients in our study that can be better elucidated with longer period of follow up and larger number of patients. In agreement with Karjalainen, et al. [4], in our non-diabetic group IHRR did not predict any of the endpoints at the short term follow up period of 6 months.

Strengths and Limitations: One of the strengths of this study is being a prospective study which gave us a full dataset for all population and enabled us to adjust for all confounders. Another strength is the equal participation rate of both diabetics and non-diabetics. Moreover our results are more practical as the study was performed while patients are taking their medicines. Limitations of the current study include the relatively small sample size, being a single centre study and the participation rate was not equal between males and females as most of our population were males (71 males / 29 females). Another limitation is that the study was completed while most of patients are taking beta blockers which could have affected the results. We continued beta blockers for ethical issues and because beta blockers withdrawal have a well-known deleterious effects. However, previous studies concluded that beta blockers have minimal or non-significant effect on HRR [4, 36].

CONCLUSION

Our results suggest that age, presence of T2D, resting HR, and diastolic LV dysfunction were the significant determinants of HRR among IHD patients undergoing PCI. In T2D group resting HR, LA size and TG level were the significant determinants of HRR. In non diabetics, the only significant determinant of HRR was the Resting HR. IHRR did predict both mortality and VT/VF at short term follow up. In patients with T2D IHRR did predict the occurrence of a CV composite end point. In non diabetics IHRR did not predict any of the endpoints at the short term follow up period of 6 months.

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