Traditional risk factors as determinants of heart rate recovery in patients with diabetes mellitus type 2 without known coronary artery disease

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Abstract. The impact of Traditional risk factors on heart rate recovery (HRR) has not been studied in patients Diabetes Mellitus type 2 without known coronary artery disease (CAD). For this reason, we sought to determine the association between HRR as cardiac autonomic dysfunction marker and traditional risk factors. The study was conducted with a cross-sectional study involving 89 patients with Type 2 Diabetes Mellitus without known having coronary artery disease. The data was taken through anamnese and laboratory tests, and subjects who met the criteria were tested for a treadmill exercise to assess heart rate recovery in the first minute. In bivariate analysis Dyslipidemia, Hypertension, smoker, age, duration of DM≥ 5 years, HbA1C ≥7.5, Peak Heart rate, functional capacity and ST depression ischemic have an association with heart rate recovery. In multivariate analysis patients with hyper triglyceride, smoker, overweight, duration of diabetes ≥ five years and HbA1C ≥ 7.5 have lower heart rate recovery significantly. Traditional risk factors are determinant factors for heart rate recovery in patients with Diabetes Mellitus type 2 without known coronary artery disease.

Keywords: Cardiac disease prevention, cardiac autonomic dysfunction, exercise test

1.Introduction
Diabetes Mellitus is an important and independent risk factor for cardiovascular mortality and morbidity [1]. Most patients with DM develop autonomic neuropathy, which is one of the more common complications in this population. Fifteen studies that use different end points reported prevalence rates of 1% to 90% for its incidence [2]. Damage to autonomic nerve fibers that innervate the heart and blood vessels consequently lead to abnormalities in heart rate (HR) control and vascular dynamics [3]. Comparatively, the mortality of DM patients manifesting an autonomic neuropathy is markedly higher than DM patients without autonomic neuropathy [4,5].

Abnormal heart rate recovery (HRR) after exercise is an easy to measure marker of reduced parasympathetic activity. It has been found to be an independent predictor of mortality in submaximal as well as in symptom-limited exercise stress testing [6,7]. HRR is defined as the reduction in heart rate from the peak of strenuous exercise to 1 min after termination of exercise. It is a new index clinically significant in evaluating the cardiac autonomic system, especially the parasympathetic
nervous function after exercise. Panzer et al reported that abnormal HRR was present among 42% of patients with impaired fasting glucose and 50% with diabetes [8]. HRR is considered as a strong predictor of increased cardiovascular disease and overall mortality, independently of other cardiac risk factors [9]. Several studies have also shown that abnormal HRR is a predictor of poor prognosis in patients with heart failure [10,11]. In addition, abnormal HRR is associated with severity of coronary artery disease [12].

However, patients with Type 2 Diabetes Mellitus (T2DM) have typically many shared complications, e.g., obesity and hyperlipidemia, which can be considered to be risk factors of T2DM rather than its consequences and which are known to affect in HRR in non-diabetic population [13,14]. Also reduced physical activity level and low physical fitness, which is associated with blunted HRR in a healthy population are common among patients with T2DM [13,15,16]. We, therefore hypothesized that HRR of T2DM patients might not be altered only because of the disease itself or its related comorbidities but also because of other earlier risk factors, e.g., obesity, hypertension, hyperlipidemia and lifestyle etc smoker, age, with low physical activity. In the present study, we examined the association between cardiovascular autonomic function as assessed by HR recovery after exercise and other potential factors, including demographic characteristics, metabolic variables that we conclude as traditional risks for coronary disease among patients with T2DM with unknown coronary artery disease (CAD).

2. Methods
The population of the present study consisted of 89 consecutive participants with T2DM who underwent treadmill exercise with Bruce protocol. The subjects for the study were male 67 (75%), and female 22 (25%), mean age 55±7.5 year, were volunteers for a routine health check-upon the Cardiac Centre of Haji Adam Malik Hospital, Medan, Indonesia. The subject’s past medical histories were obtained through an amanessis. Those who had history of stroke, disability, COPD, established heart disease, and the other chronic heart disease were exlcluded. Subjects with hypertensive or on antihypertensive medication except for beta blocker dan Calcium channel blockers (CCB) non dyhidropiridine (DHP) were included in the study. We obtained written consents from all subjects, and the study was approved by Adam Malik Hospital and University of Sumatera Utara Medical School Institutional Review Board.

2.1 Demographic and Laboratory tests
Blood sampling for serum lipid profile and glucose was obtained after at least 14 hr of fasting. Post prandial blood glucose obtained after 2 hours meal. Diabetes Mellitus (symptom of diabetes and plasma glucose concentration ≥200 mg/dl or fasting plasma glucose ≥126 mg/dl or 2 hp >200 mg/dl) was diagnosed based on laboratory, patients information and medical history. Traditional risk defines as dyslipidemia, smoker, age >55 years, hypertension and obesity. As for Diabetes status, we include blod glucose control (HbA1C) and time duration the subject established with T2DM. Subjects were defined by their smoking habits as current or nonsmokers. Ex-smokers were considered those who quit smoking for at least 3 years. Body weight and height were measured in light clothing, and body mass index (BMI) was calculated. Hypertension was defined according to the current guidelines [17].

2.2 Treadmill Exercise Protocol
Treadmill exercise stress test was done in all subjects using the Bruce protocol. Blood pressure, HR and the Borg scale of rating of perceived exertion (RPE) 20 were measured at 2 minute of each stage of the exercise [17]. The exercise was stopped when the subject demanded cessation of the treadmill due to exhaustion, or if the heart rate achieved was more than 85% of estimated maximal HR (220-age), or if the RPE was more than 18. During the recovery phase, the subjects continued to walk for 30 second at the speed of 1.2 mph and then they sat down for 5 min with continued medical monitoring. HRR was calculated as the decrease of HR per minute between the peak exercise period and 1 min post exercise. Abnormal HRR define as the reduction of heart rate ≤ 12 b.p.m from peak
heart rate to 1 minute after the termination of exercise. Those subjects who showed malignant arrhythmia, severe hypertension or hypotension, or unfinished exercise due to neuromuscular problem during exercise were excluded from this study. Positive myocardial ischemia was defined as horizontal or downsloping ST segment depression of ≥ 0.1 mV for 80 ms in 3 consecutive beats.

2.3 Statistical Analysis
Data with normal distribution expressed as a mean ± standard deviation and the others expressed as a median (lower-upper) value. Comparisons of means between the two groups were made by using a Student t-test. Bivariate analysis between variables was evaluated by Chi square. Regression logistic model was constructed with HRR as the dependent variable, and independent variables were those variables showing significant association with HR recovery upon uni and bivariate analysis. Back stepwise regression was used for the final model selection. Criteria for stepwise regression was 0.25 to included in multivariate analysis. Association between the independent variables was explored and insignificant association terms were removed from the final model. A p value <0.05 was considered statistically significant. SPSS 18 for was used for the analysis.

3. Results
Clinical Characteristic Demographic and laboratory characteristics of the population are shown in Table 1. The population study was around 55±7.39 years old. Half of the subjects had a sedentary lifestyle, with only 50.2 % doing regular exercise more than three times per week. Fifty-eight percent of the subjects reported that they were either hypertensive or on antihypertensive medications. Fifty-eight point one percent were smokers, and 63% subjects have dyslipidemia. There is significant different value in Lipid profile (HDL-c, LDL-c, TG ) between subject with abnormal HRR (≤12 b.p.m) and normal HRR (>12 b.p.m). In Diabetic profile, there are significant different value in HbA1C, fasting blood glucose and Duration of T2DM between normal and abnormal HRR. The BMI also show a significant between both of the group 27 (12.8-35) VS 24 (19-29), p = 0.001. As is shown in Table 2, these Treadmill test variables display a significant difference between those with abnormal and normal HRR proportion of peak heart rate, Mets, Chronotropic Incompetence, were different between the two groups

| Characteristic | Heart Rate Recovery | All patients | P Value |
|----------------|---------------------|-------------|---------|
|                | ≤12 b.p.m N=46 | >12 b.p.m N=43 |                |
| Age (median), years | 57±6.5 | 52±7.39 | 55±7.5 | 0.001 |
| Male | 34(38%) | 33(37.5%) | 67(75%) | 0.760 |
| Hypertension | 35(38%) | 17(19%) | 52(58%) | 0.001 |
| Smoker | 27(30%) | 11(28.9%) | 38(58.9%) | 0.003 |
| Dyslipidemia | 35(38%) | 23(25%) | 58(63%) | 0.01 |
| HDL-c (mg/dl) | 38.6 ±4.7 | 48 ±7.42 | 43±6.9 | 0.003 |
| LDL-c (mg/dl) | 178(92-265) | 132(90-211) | 156(90-265) | 0.045 |
| TG (mg/dl) | 197±51 | 141±46 | 170±56 | 0.031 |
| Total Cholesterol | 241(156-376) | 196(167-319) | 212(156-376) | 0.076 |
| HbA1C | 8.2(6.4-11.6) | 6.5(6-10.2) | 7.5(6-11.6) | 0.001 |
| Duration of T2DM | 6 (3-10) | 4(1-7) | 4(1-10) | 0.034 |
| FPG (mg/dl) | 147±46 | 119±28 | 135±51 | 0.02 |
| 2h post prandial glucose (mg/dl) | 212(133-332) | 178(121-245) | 210 ± 51.9 | 0.001 |
| Variable                  | Heart Rate Recovery | All patient | P Value |
|---------------------------|---------------------|-------------|---------|
|                           | ≤12b.p.m.           | >12b.p.m.   |         |
| Peak Heart Rate           | 136(76-187)         | 156(111-178)| 148(76-178) | 0.001 |
| Peak Sistolic BP (mmHg)   | 179.2±28.11         | 179.6±21.34 | 179±24.9 | 0.92  |
| Peak Diastolic BP (mmHg)  | 79(58-126)          | 77(65-118)  | 77(58-126) | 0.86  |
| Mets                      | 7(1.8-10.2)         | 9.2(5-11)   | 7.6(1.8-11) | 0.001 |
| Duration Treadmil test (minute) | 5.09(2.4-9.5) | 6.57(3.4-10.49) | 6.4(2.4-10.49) | 0.002 |
| Chronotropic Incompetence | 25(28%)             | 7(7%)       | 32(35%)  | 0.001 |
| ST depression positive    | 21(23%)             | 5(5.6%)     | 26(29%)  | 0.001 |

**Table 2. Characteristic Treadmill Test Result**

BP: Blood Pressure; Mets: Metabolic Equivalents

In Bivariate analysis as in Table 3 and 4, subjects who older than 55 years old [OR 4.81 (1.95-12.12)], hypertension [OR 4.81(1.954-12.12)], smoker [OR 4.13(1.667-10.19)], dyslipidemia [OR 4.76(1.12-6.8)], HDL-c <40 [OR 4.71(1.74-12.73)], LDL-c ≥130 [OR 2.7(1.12-6.58)], TG ≥150 [OR 8.31(3.13-21.60)], BMI≥25 [OR 4.24(1.35-8.01)] have higher probability to get abnormal heart rate recovery. HbA1C ≥7.5 has higher probability to abnormal heart rate recovery [OR 1.31 (4.6-36.4)], p=0.005 as seen in duration of diabetes ≥5 years [OR 6.86(2.46-18.30)], p=0.012.

By multivariate analysis in table 5, the presence of Triglyceride ≥150, smoker, BMI ≥25, HbA1C ≥7.5, Duration of DM ≥ 5 years were independently associated with slower HRR after an adjustment for the other variables. Peak heart rate and ischemic response in treadmill test also give a significant association with delay of HRR.
Table 3. Bivariate Analyses between HRR and Traditional Risk Factors

| Variable | Heart Rate Recovery | P  | OR  | CI      |
|----------|---------------------|----|-----|---------|
|          | ≤12 b.p.m | >12 b.p.m |     |         |         |
| Age (years) |         |           |     |         |         |
| • ≥55      | 28 (68.3%) | 13 (31.7%) | 0.04 | 3.59  | 1.48-8.54 |
| • <55      | 18 (37.5%) | 30 (62.5%) |     |        |         |
| Gender  |          |           |     |         |         |
| • Male    | 34 (50.7%) | 33 (49.3%) | 0.76 | 0.89  | 0.32-2.25 |
| • Female  | 12 (54.5%) | 10 (45.4%) |     |        |         |
| Hypertension |         |           |     |         |         |
| • Yes     | 35 (67.3%) | 17 (32.7%) | 0.001 | 4.81  | 1.954-12.12 |
| • No      | 11 (29.7%) | 26 (70.3%) |     |        |         |
| Smoker    |          |           |     |         |         |
| • Yes     | 27 (71.1%) | 11 (28.9%) | 0.003 | 4.13  | 1.667-10.19 |
| • No      | 19 (37.3%) | 32 (62.7%) |     |        |         |
| Dyslipidemia |         |           |     |         |         |
| • Yes     | 41 (59.4%) | 28 (40.6%) | 0.001 | 4.76  | 1.12-6.8 |
| • No      | 5 (25%) | 15 (75%) |     |        |         |
| Lipid Profile |         |           |     |         |         |
| • HDL-c ≤40 | 22 (75.9%) | 7 (24.1%) | 0.02 | 4.71  | 1.74-12.7 |
| • HDL-c >40 | 24 (40%) | 36 (60%) |     |        |         |
| • LDL-c ≥130 | 34 (60.7%) | 22 (39.3%) | 0.03 | 2.7  | 1.12-6.58 |
| • LDL-c <130 | 12 (36.4%) | 21 (63.6%) |     |        |         |
| • TG ≥150  | 36 (80%) | 9 (20%) | 0.001 | 8.31  | 3.13-21.6 |
| • TG <150  | 10 (22.7%) | 34 (77.3%) |     |        |         |
| • Total Cholesterol ≥200 | 34 (68.8%) | 16 (32%) | 0.04 | 4.78  | 1.93-11.7 |
| • Total Cholesterol <200 | 12 (30.8%) | 37 (69.2%) |     |        |         |
| BMI       |          |           |     |         |         |
| • ≥25     | 32 (68.1%) | 15 (31.9%) | 0.03 | 4.24  | 1.35-8.01 |
| • <25     | 14 (33.3%) | 28 (66.7%) |     |        |         |

BMI: Body Mass Index; TG: Tryglyceride; HDL: High-Density Lipoprotein cholesterol; LDL-c: Low-Density lipoprotein Cholesterol; BMI: Body Mass Index
Table 4. Bivariate Analyses between HRR and T2DM status

| Variable          | Heart Rate Recovery | P   | OR  | CI         |
|-------------------|---------------------|-----|-----|------------|
|                   | ≤12b.p.m            | >12b.p.m |    |            |
| HbA1C             |                     |     |     |            |
| • ≥7.5            | 33(80.5%)           | 17(19.5%) | 0.005 | 13.1 | 4.6 | 36.4 |
| • <7.5            | 13(26.5%)           | 26(73.5%) |     |          |    |     |
| FPG               |                     |     |     |            |
| • ≥126            | 12(26.6%)           | 33(73.3%) | 0.06 | 4.01 | 0.27 | 2.87 |
| • <126            | 34(77.3%)           | 10(22.7%) |     |          |    |     |
| 2h post prandial  |                     |     |     |            |
| • ≥200            | 28(70%)             | 12(30%) | 0.056 | 1.25 | 0.82 | 4.56 |
| • <200            | 18(36.7%)           | 31(63.3%) |     |          |    |     |
| Duration T2DM     |                     |     |     |            |
| • ≥5 years        | 26(78%)             | 7(22%) | 0.012 | 6.86 | 2.46 | 18.3 |
| • <5 years        | 20(35.7%)           | 36(64.3%) |     |          |    |     |

FPG: Fasting Plasma Glucose; T2DM: Type 2 Diabetes Mellitus

Table 5. Logistic Regression with HRR as Dependent Variable

| Variable                        | Coef | P   | OR  | CI 95%         |
|---------------------------------|------|-----|-----|----------------|
| Smoker                          | 0.801| 0.042 | 2.21 | 1.312-15.296 |
| Triglycerides                   | 1.27 | 0.015 | 3.567 | 1.378-20.23 |
| BMI                             | 0.871| 0.024 | 2.388 | 2.594-23.31 |
| Duration of T2DM                | 2.451| 0.003 | 11.09 | 2.402-53.59 |
| HBA1C                           | 2.381| 0.024 | 10.08 | 1.447-71.72 |
| Peak Heart Rate                 | -1.574| 0.015 | 0.265 | 0.006-0.913 |
| ST Depression positive ischemia | 1.412| 0.184 | 2.21  | 1.83-3.813 |

4. Discussion

As shown in table 5, Triglyceride, BMI, Smoker, Duration of T2DM, HbA1C have independent association with the abnormality of heart rate recovery as a marker of subclinical cardiac diabetic neuropathy. Peak heart rate during exercise, and positive ST depression in precordial lead also showed significant association. This result shows that traditional risk factors can determine abnormal heart rate recovery as seen in coronary artery disease. Christina et al in 2001 also showed a similar result with heart rate variability as its cardiac neuropathy marker. In a cross sectional study covered by 600 DM patients, the regression analysis showed cardiac autonomic neuropathy incidence increase with postif correlation with hypertension, smoker, duration of diabetes, LDL, Cholesterol triglyceride and HbA1C. HbA1C value in this study was 8±1.8 with p <0.05 [18]. EURODIAB study also showed that there is a correlation between cardiac autonomic dysfunction with duration of DM (cut of point 8 years), smoker and HDL-c even though we have a different marker tool to established cardiac autonomic neuropathy [19]. It is necessary, however, to bear in mind that their patients had relatively well controlled glycemic state and that only a few of them had abnormal HR recovery according to the criteria mentioned.
However our limitation is the blood sample is taken only once to evaluate association between lipid profile and blood glucose status with heart rate recovery. Only one prior study has prospectively studied the relationship of slower HRR with change in risk factor levels over time, and similarly found no association between slower HRR and an increase in levels of glucose and insulin over time [20].

5. Conclusion
In conclusion, traditional risk factor is significantly associated with impaired vagal reactivation as shown in slower heart rate recovery. Therefore, evaluation of all cardiovascular traditional risk factors is necessary to prevent cardiac autonomic dysfunction in Diabetes Mellitus patients.

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