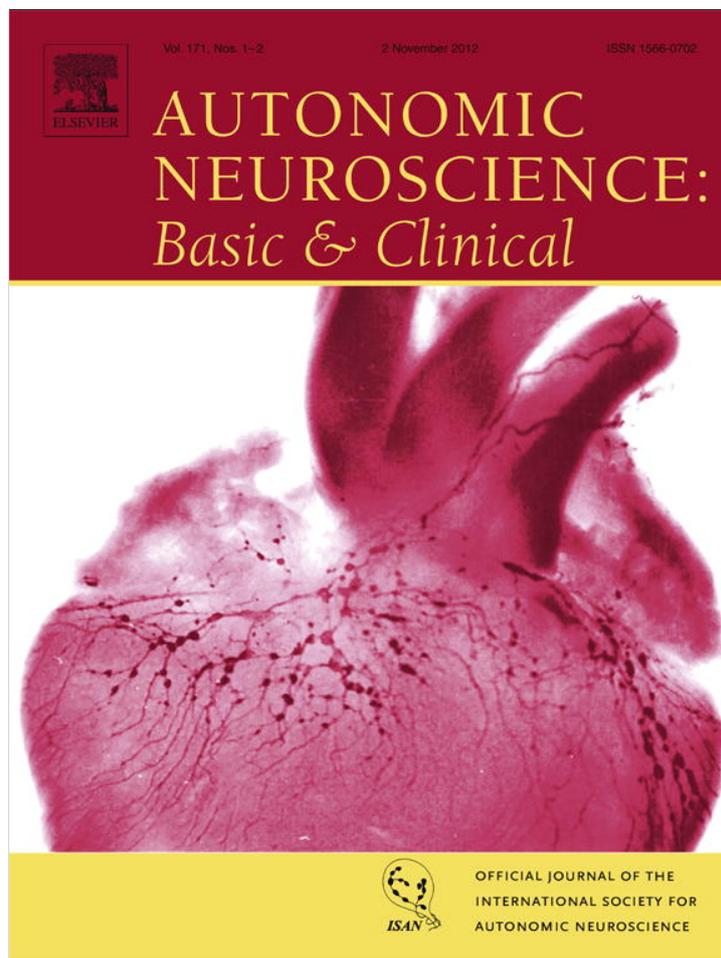


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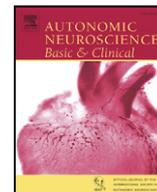
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Determinants of heart rate recovery in coronary artery disease patients with and without type 2 diabetes

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ABSTRACT

Cardiovascular autonomic dysfunction, which is a common complication of diabetes, is associated with increased mortality in patients with coronary artery disease (CAD). However, the reasons of autonomic dysfunction in CAD patients with or without diabetes are not well known. We examine the association between heart rate recovery (HRR) and other potential factors among CAD patients with and without type 2 diabetes (T2D). Correlations between HRR 60 s after exercise (HRR₆₀), characteristics, laboratory and echocardiographic variables, exercise capacity and physical activity were assessed in 50 CAD patients with T2D and 55 patients with CAD alone. HRR₆₀ had the closest univariate correlation with physical activity and exercise capacity in patients with T2D ($r = 0.38$, $p = 0.006$ and $r = 0.37$, $p = 0.008$, respectively). Age, exercise capacity and high-density lipoprotein cholesterol level explained 30% of the HRR₆₀ in patients with T2D ($p = 0.001$), while the high intensity physical activity was the only predictor of HRR₆₀ in CAD patients (12%, $p = 0.010$). HRR₆₀ was reduced in patients with T2D as compared with those without (34 ± 9 vs. 39 ± 9 bpm, $p = 0.005$), but the difference was no longer significant after adjustments for physical activity, exercise capacity, body mass index and the use of calcium antagonists and nitrates ($p = 0.273$). In conclusion, blunted HRR is more common among CAD patients with T2D than in those without, and this is more closely related to physical activity and obesity than to the duration of T2D or associated co-morbidities.

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1. Introduction

Type 2 diabetes (T2D) is associated with abnormal cardiovascular autonomic function (Vinik et al., 2003; Schroeder et al., 2005; Schonauer et al., 2008), which can be assessed e.g. by measurement of post-exercise heart rate (HR) recovery (Okutucu et al., 2011). There is increasing evidence, that blunted HR recovery during the first minutes after the cessation of exercise is a predictor of non-fatal and fatal cardiovascular events in the general population and in various patient groups, including patients with T2D (Cole et al., 1999; Lauer and Froelicher, 2002; Cheng et al., 2003; Nissinen et al., 2003; Jouven et al., 2005; Chacko et al., 2008; Georgoulis et al., 2009).

It has been suggested that impaired HR recovery may be related to the poor glycemic control and severity of diabetes itself (Cheng et al., 2003; Seshadri et al., 2003; Fang et al., 2005; Georgoulis et al., 2009), or to co-morbidities, such as macrovascular myocardial ischemia and

coronary artery disease (CAD) (Cheng et al., 2003; Georgoulis et al., 2007; Yamada et al., 2011) or microvascular complications like retinopathy and nephropathy (Kramer et al., 2008; Almeida et al., 2011). However, patients with T2D have typically many shared complications e.g. obesity and hyperlipidemia, which can be considered to be risk factors of T2D rather than its consequences and which are known to affect in HR recovery in non-diabetic population (Georgoulis et al., 2003; Kimura et al., 2006). Also reduced physical activity level and low physical fitness, which are associated with blunted HR recovery in healthy population (Carnethon et al., 2003; Georgoulis et al., 2003; Carnethon et al., 2005), are common among patients with T2D (Hays and Clark, 1999; Nelson et al., 2002). We therefore hypothesized that HR recovery of T2D patients may not be altered only because of disease itself or its related co-morbidities but also because of other earlier risk factors e.g. obesity, hyperlipidemia and sedentary lifestyle 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, echocardiographic parameters, severity of microvascular and macrovascular disease, markers of inflammation, the level of spontaneous daily physical activity and exercise capacity among CAD patients with and without T2D. We hypothesized that

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physical activity of the patients with T2D might be an important factor influencing the level of autonomic regulation.

2. Methods

2.1. Subjects and protocol

The work described here is part of a larger ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection) study taking place in the Division of Cardiology at Oulu University Hospital (Oulu, Finland) and the Department of Exercise and Medical Physiology at Verve (Oulu, Finland). The ARTEMIS study is registered at ClinicalTrials.gov, Record 1539/31/06. CAD patients with T2D ($n=50$, 8 women) and CAD patients without T2D ($n=55$, 11 women) were selected from the ARTEMIS database observing the following exclusion criteria: advanced age (>75 years), body mass index (BMI) >40 kg/m², NYHA class III or IV, left ventricular ejection fraction $<40\%$, scheduled cardiac revascularization therapy, heart failure, unstable angina pectoris, severe peripheral atherosclerosis, or inability to perform an exercise stress test, e.g. due to musculoskeletal problems. Pre-diabetes (impaired glucose tolerance and impaired fasting glucose) was excluded from the patients without T2D by means of an oral glucose tolerance test (WHO, 1999).

T2D was verified according to the current criteria (WHO, 1999). Patients who had a fasting plasma glucose level ≥ 7.0 mmol/l or were on hypoglycemic medication based on a prior diagnosis of diabetes were classified as having T2D. CAD and its severity were assessed by measurement of the Syntax score in coronary angiography (Sianos et al., 2005), and left ventricular systolic and diastolic function by 2-D and tissue Doppler echocardiography. Blood samples and urine samples were obtained for the analysis of renal function, microalbuminuria, inflammation markers, blood lipids, plasma glucose and glycated hemoglobin (HbA1c) levels (Oulu University Hospital, Oulu, Finland). Depression score was defined using Depression Scale (DEPS) which is self-rating depression scale.

The following protocol was performed in the Department of Exercise and Medical Physiology at Verve (Oulu, Finland). Blood pressure was measured (average of two measures) in a supine position after a 10-min resting period (Tango, Sun-Tech, Raleigh, NC, USA). The patients performed an incremental symptom-limited maximal exercise test on a bicycle ergometer (Monark Ergomedic 839 E, Monark Exercise AB, Vansbro, Sweden) for the assessment of peak oxygen uptake and maximal exercise capacity. The test was started at 30 W, and the work rate was increased by 15 W in men and 10 W in women every minute until voluntary exhaustion or ST segment depression >0.2 mV in electrocardiogram (only one subject in both groups). Ventilation and gas exchange (M909 Ergospirometer, Medikro, Kuopio, Finland) were monitored continuously during the test. The highest 1-min mean value of oxygen consumption was taken to express peak oxygen uptake. Maximal workload and exercise capacity were calculated as the average workload and metabolic equivalents (METs) during the last minute of the test. Relative exercise capacity was expressed as a percentage of the predicted exercise capacity, which was calculated using the following formula: $EC_{pred} = 18 - (0.15 \cdot \text{age})$ for men and $14.7 - (0.13 \cdot \text{age})$ for women (Kim et al., 2007). The patients moved to a supine position immediately after the cessation of exercise. A 15-lead electrocardiogram (GE Healthcare, CAM-14, Freiburg, Germany) and R-R intervals (Polar Electro, Kempele, Finland) were recorded during exercise and in a supine position 10 min after exercise.

The subjects were not allowed to eat or to drink coffee for 3 h before the tests. Strenuous physical activity and alcohol consumption were prohibited on the day of the test and the preceding day. The study was performed according to the Declaration of Helsinki, the local research ethics committee of the Northern Ostrobothnia Hospital District approved the protocol and all the subjects gave their written informed consent.

2.2. Heart rate recovery

R-R intervals were recorded at a sampling frequency of 1000 Hz (Polar Electro, Kempele, Finland) and the maximal HR was calculated as a mean value of 5 R-R intervals before cessation of exercise from the Polar R-R interval data and converted to maximal HR in beats·min⁻¹ with the following equation: maximal HR (beats·min⁻¹) = $60 \cdot (\text{mean R-R interval in ms} \cdot 1000^{-1})^{-1}$. HR recovery values were calculated from the Polar data as mean values of 5 R-R intervals around the time points 15, 30, 60 (HRR₆₀) and 120 (HRR₁₂₀) seconds after cessation of exercise. Thereafter, HR recovery (beats·min⁻¹) was calculated as the change in HR from maximal HR to recovery HR at the time points of 15, 30, 60, and 120 s after the cessation of exercise. The slope of HR during the 60 s after cessation of exercise (HRR_{slope}) was calculated according to a linear model using the above-mentioned HR values at the maximum and at the 15, 30 and 60 s time points.

2.3. Measurement of physical activity

Physical activity was measured during waking hours over five consecutive days, including weekends, with a wristwatch equipped with a one-dimensional accelerometer (Polar AW200 Activity Watch; Polar Electro Oy, Kempele, Finland). All the subjects were advised to carry on their normal daily routine during the measurement days. The accelerometer technology has recently been validated and compared with energy expenditure measured by indirect calorimetry (Brugniaux et al., 2010). Physical activity time (METs ≥ 2) per day was analyzed separately for moderate (METs = 2–5, “slow walking or walking”) and high intensity (METs >5 “brisk walking or higher”).

2.4. Statistical analyses

A Kolmogorov–Smirnov Z-test was performed for all variables to assess the assumption of a Gaussian distribution. The unpaired Student's t-test was used to assess the differences between the CAD patients with and without T2D in normally distributed data. The Mann–Whitney U-test was used for the between-group comparisons of variables having a non-Gaussian distribution, and the chi-square test was used for comparing categorical variables. Significant differences in HR recovery between the groups were adjusted for daily physical activity time, exercise capacity and BMI using ANCOVA. Since some of the data were skewed, a Spearman's nonparametric test was used to assess the correlations between HR recovery and potential predictors, including demographic characteristics, laboratory measurements, echocardiographic parameters, severity of microvascular and macrovascular disease, markers of inflammation, the level of spontaneous daily physical activity and exercise capacity in the CAD patients with and without T2D.

Linear regression analyses with stepwise regression analyses were used to construct the predictive regression models for HR recovery in the patient groups. Since the HR recovery 1 min after exercise is widely used time point when defined abnormal HR recovery in prognostic studies (Cole et al., 1999; Nishime et al., 2000; Jouven et al., 2005; Chacko et al., 2008; Georgoulis et al., 2009), this was chosen as a representative variable for HR recovery in linear regression analyses. The variables which correlated with the HRR₆₀ in the Spearman's correlation analyses ($p < 0.05$) were included as covariates in the linear regression analyses. All the significant demographic, laboratory and echocardiographic variables, excluding medication, were included in the first block of the linear regression analysis (Model I), while medication was added as the second block to the final model (Model II) to find the predictors that maximized the R value. The statistical analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, USA). A p value < 0.05 was considered statistically significant.

3. Results

3.1. Descriptive results

Demographic characteristics of population, including comparisons between the patients with and without T2D, are presented in Table 1. The CAD patients with T2D were more obese (weight, BMI, waist-hip ratio), had higher fasting plasma glucose and HbA1c levels, triglyceride concentrations and creatinine clearance than the CAD patients

Table 1
Demographic characteristics of the patients.

	CAD + T2D (n = 50)	CAD (n = 55)	p value between groups
Sex (M/F)	42/8	44/11	0.595
Age, year	61 ± 6	62 ± 6	0.696
Height, m	1.73 ± 0.08	1.71 ± 0.08	0.491
Weight, kg	90 ± 14	79 ± 11	<0.001
Body mass index, kg/m ²	30.3 ± 3.9	27.0 ± 3.1	<0.001
Waist-hip ratio	1.01 ± 0.06	0.95 ± 0.08	<0.001
Systolic blood pressure, mm Hg	134 ± 14	136 ± 16	0.463
Diastolic blood pressure, mm Hg	81 ± 10	82 ± 7	0.429
History of acute myocardial infarction			
NSTEMI	14 (28%)	21 (38%)	0.269
STEMI	12 (24%)	13 (24%)	0.965
Revascularization			
Percutaneous coronary intervention	30 (60%)	33 (60%)	1.000
Coronary artery by-pass grafting	14 (28%)	16 (29%)	0.902
Syntax score	6.0 ± 6.8	3.1 ± 4.0	0.039
Left ventricular ejection fraction, %	67 ± 8	66 ± 8	0.281
Left ventricular end diastolic diameter, mm	50 ± 6	51 ± 5	0.642
Left ventricular mass index	100.0 ± 21.7	98.9 ± 21.9	0.792
E/E'	9.61 ± 3.40	9.08 ± 2.58	0.364
Exercise capacity, METs	6.8 ± 1.7	7.8 ± 1.8	0.006
Relative EC, % per predicted METs	80 ± 19	94 ± 20	<0.001
Maximal heart rate, bpm	130 ± 19	133 ± 18	0.349
Heart rate reserve, bpm	73 ± 22	79 ± 18	0.111
Diabetic retinopathy	3 (6%)	0 (0%)	0.065
Current smokers	3 (6%)	7 (13%)	0.241
Depression score	4.4 ± 3.8	4.7 ± 4.5	0.809
Laboratory analyses			
Glycated hemoglobin, %	6.0 ± 0.7	5.5 ± 0.2	<0.001
Fasting plasma glucose, mmol/l	7.1 ± 1.6	5.4 ± 0.5	<0.001
Total cholesterol, mmol/l	3.9 ± 0.7	3.9 ± 0.7	0.995
HDL cholesterol, mmol/l	1.1 ± 0.3	1.2 ± 0.3	0.037
LDL cholesterol, mmol/l	2.2 ± 0.5	2.2 ± 0.6	0.583
Triglycerides, mmol/l	1.9 ± 1.1	1.2 ± 0.5	<0.001
High-sensitivity C-reactive protein, mg/l	1.6 ± 1.7	2.0 ± 4.2	0.222
Creatinine clearance, ml/min	118.8 ± 34.3	97.8 ± 22.3	<0.001
Microalbuminuria, mg/l	15.5 ± 30.7	8.0 ± 8.5	0.022
Albumin-creatinine ratio, mg/mmol	1.7 ± 3.4	0.9 ± 0.9	0.630
Physical activity			
Daily PA time, h/day	2:48 ± 1:24	3:15 ± 1:15	0.087
PA at moderate intensity, h/day	2:46 ± 1:23	3:10 ± 1:13	0.113
PA at high intensity, min/day	2:16 ± 3:14	4:48 ± 9:12	0.139
Medication			
Beta blockers	50 (100%)	55 (100%)	1.000
ACEI/ARB	33 (66%)	33 (60%)	0.525
Statin	48 (96%)	50 (91%)	0.296
Anticoagulants	49 (98%)	54 (98%)	0.946
Calcium antagonists	16 (32%)	6 (11%)	0.008
Nitrates	21 (42%)	8 (15%)	0.002
Diuretics	18 (36%)	13 (24%)	0.165
Medication for type 2 diabetes			
No medication	8 (16%)		
Oral medication	37 (74%)		
Insulin	5 (10%)		

Values are means ± SD or number of subjects (%); CAD, coronary artery disease; T2D, type 2 diabetes; n, number of subjects; NSTEMI, no-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; Syntax score, a lesion-based angiographic score after revascularization; E/E', ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; METs, metabolic equivalents; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PA, physical activity; ACEI, angiotensin conversion enzymes inhibitor; ARB, angiotensin receptor blocker; ACEI/ARB, patients taking at least one of these.

($p < 0.001$ for all). They also had lower exercise capacity and high-density lipoprotein (HDL) cholesterol levels and higher Syntax scores and urine albumin concentrations ($p < 0.05$ vs. the CAD patients). Blood pressure, echocardiographic parameters, history of acute myocardial infarction, maximal HR, HR reserve, smoking habits and inflammatory markers did not differ between the groups (Table 1). Calcium antagonists and nitrates were used more commonly by the CAD patients with T2D than by those with CAD alone (Table 1). The mean duration of diabetes was 62 ± 85 months.

3.2. Determinants of heart rate recovery

In the patients with diabetes, HRR_{60} correlated with daily physical activity time ($r = 0.38$, $p = 0.006$), exercise capacity ($r = 0.38$, $p = 0.007$) and relative exercise capacity ($r = 0.37$, $p = 0.008$, Table 2, Fig. 1), and physical activity time, exercise capacity and relative exercise capacity were also correlated with HRR_{120} . Additionally, there was a positive correlation between HRR_{60} and the HDL cholesterol level ($r = 0.31$, $p = 0.018$). HRR_{60} was negatively correlated with age ($r = -0.36$, $p = 0.010$) and left ventricular ejection fraction ($r = -0.29$, $p = 0.042$), but not with other echocardiographic parameters. Moreover, HRR_{60} did not correlate with the duration of T2D, fasting plasma glucose and HbA1c level, Syntax score, albuminuria, or high-sensitivity C-reactive protein level in the patients with T2D (Table 2). HRR_{60} did not differ in the patients with diabetes and history of myocardial infarction as compared with counterparts without myocardial infarction (35 ± 9 vs. 32 ± 9 bpm, $p = 0.225$). Patients with diabetes who used diuretics or calcium antagonists had reduced HR recovery compared with ones who did not take these drugs

Table 2

Correlations of heart rate recovery 60 s after cessation of exercise with demographic characteristics, features of type 2 diabetes, microvascular and macrovascular complications, laboratory measurements and echocardiographic parameters in coronary artery disease patients with and without type 2 diabetes.

	CAD + T2D (n = 50)	CAD (n = 55)
Demographic characteristics		
Age	-0.36, $p = 0.010^*$	-0.17, $p = 0.218$
Body mass index	-0.21, $p = 0.129$	-0.10, $p = 0.460$
Systolic blood pressure	-0.04, $p = 0.769$	-0.09, $p = 0.511$
Diastolic blood pressure	0.17, $p = 0.239$	0.11, $p = 0.441$
Exercise capacity	0.38, $p = 0.007^{**}$	0.08, $p = 0.550$
Relative exercise capacity	0.37, $p = 0.008^{**}$	0.09, $p = 0.496$
Daily physical activity time	0.38, $p = 0.006^{**}$	-0.09, $p = 0.535$
Physical activity at high intensity	0.09, $p = 0.539$	0.44, $p = 0.001^{***}$
Depression score	0.09, $p = 0.535$	-0.39, $p = 0.003^{**}$
Features of type 2 diabetes		
Duration of type 2 diabetes	-0.25, $p = 0.084$	0.15, $p = 0.272$
Fasting plasma glucose	-0.17, $p = 0.250$	
Glycated hemoglobin	-0.27, $p = 0.063$	-0.26, $p = 0.060$
Microvascular and macrovascular complications		
Albuminuria	-0.24, $p = 0.096$	-0.02, $p = 0.893$
Creatinine clearance	0.12, $p = 0.418$	0.09, $p = 0.525$
Albumin-creatinine ratio	-0.09, $p = 0.543$	-0.18, $p = 0.182$
Syntax score	0.05, $p = 0.742$	0.14, $p = 0.324$
Inflammation		
high-sensitivity C-reactive protein	-0.14, $p = 0.338$	-0.01, $p = 0.919$
Lipid profile		
Total cholesterol	0.14, $p = 0.319$	-0.25, $p = 0.066$
HDL cholesterol	0.31, $p = 0.028^*$	-0.11, $p = 0.435$
LDL cholesterol	0.08, $p = 0.606$	-0.26, $p = 0.054$
Triglycerides	-0.11, $p = 0.438$	-0.23, $p = 0.099$
Cardiac function		
Left ventricular ejection fraction	-0.29, $p = 0.042^*$	0.14, $p = 0.306$
E/E'	0.01, $p = 0.940$	-0.06, $p = 0.669$

CAD, coronary artery disease; T2D, type 2 diabetes; n, number of subjects; Syntax score, a lesion-based angiographic score; HDL, high-density lipoprotein; LDL, low-density lipoprotein; E/E', ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; * $p < 0.05$; ** $p < 0.001$.

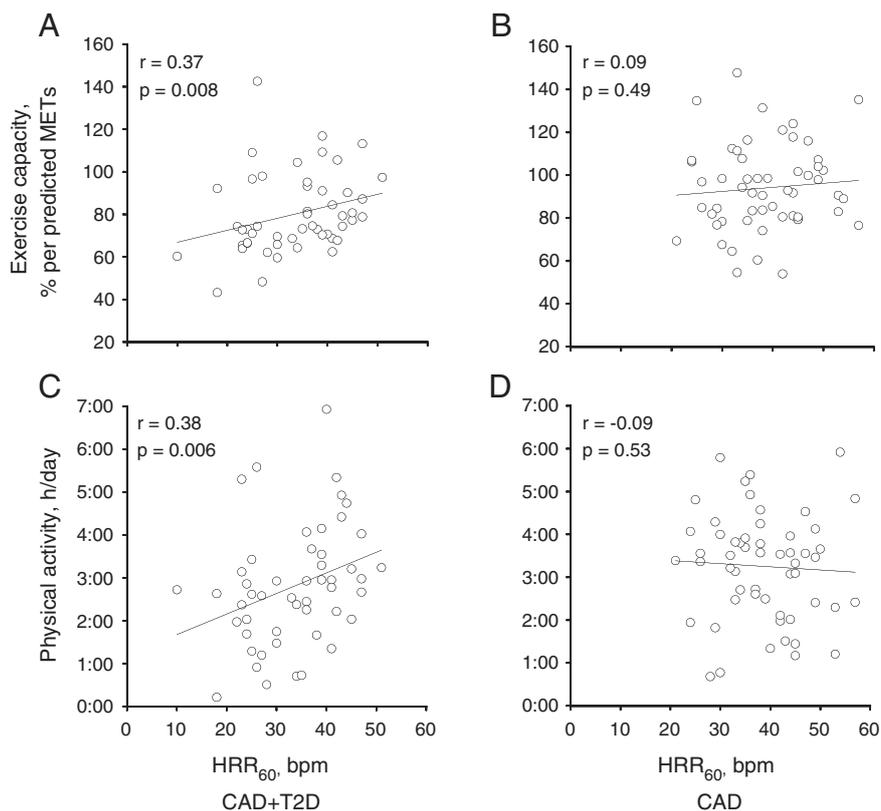


Fig 1. Correlation of relative exercise capacity (% per predicted METs) (A and B) and daily physical activity time (C and D) with heart rate recovery 60 s after cessation of exercise (HRR₆₀) among coronary artery disease patients without (CAD) and with type 2 diabetes (CAD + T2D).

(29 ± 9 vs. 36 ± 8 bpm, p = 0.003 and 29 ± 9 vs. 36 ± 9 bpm, p = 0.018 for users and non-users of diuretics and calcium antagonists, respectively).

In the CAD patients without T2D there was a clear positive correlation between HRR₆₀ and the amount of high intensity physical activity (r = 0.44, p = 0.001), while a significant negative correlation was found between HRR₆₀ and the depression score (r = -0.39, p = 0.003) (Table 2). No other correlations were observed between the HRR₆₀ and the measured variables in this patient group.

The linear regression analyses showed age, relative exercise capacity and HDL cholesterol level to be significant predictors of HR recovery in Model I for the patients with T2D (R = 0.55, R² = 0.30, p = 0.001) (Table 3), but when relative exercise capacity and daily physical activity time were included in the same model without any other variables, the physical activity time was the only predictor of HR recovery, with an R value of 0.32 (R² = 0.10, p = 0.025). When medication was included in the analysis, in Model II, the predictors of HR recovery were age, relative exercise capacity, HDL cholesterol level and the use of diuretics, with an R value of 0.61 (R² = 0.37, p < 0.001). Physical activity at high intensity was the only predictor of HRR₆₀ among the CAD patients without T2D in Models I and II, with R values of 0.35 (R² = 0.12, p = 0.010) (Table 3).

3.3. Heart rate recovery

The CAD patients with T2D had reduced HRR₆₀ (34 ± 9 vs. 39 ± 9 bpm, p = 0.005), HRR₁₂₀ (44 ± 13 vs. 50 ± 10 bpm, p = 0.019), and HRR_{slope} (-0.55 ± 0.16 vs. -0.63 ± 0.15 beats/s, p = 0.007) compared to the CAD patients without T2D. After adjustment for daily physical activity time, exercise capacity, BMI, and the use of calcium antagonists and nitrates there were no significant differences between the groups in any of these three measures (p = 0.273, p = 0.584 and p = 0.485, respectively).

4. Conclusions

The results showed that the CAD patients with T2D have reduced post-exercise HR recovery compared with the CAD patients without

Table 3
Linear regression analyses with HRR₆₀ as the dependent variable in coronary artery disease patients with and without type 2 diabetes.

	HRR ₆₀		
	(Partial) R	(Partial) R ²	p value
CAD + T2D patients			
Model I	0.55	0.30	0.001
Included variables			
Age	-0.41	0.17	0.004
HDL cholesterol	0.30	0.09	0.040
Relative exercise capacity	0.34	0.12	0.020
Excluded variables			
Left ventricular ejection fraction	-0.15	0.02	0.311
Daily physical activity time	0.06	0.00	0.710
Model II	0.61	0.37	<0.001
Included variables			
Age	-0.37	0.14	0.012
HDL cholesterol	0.29	0.08	0.046
Relative exercise capacity	0.25	0.06	0.086
Diuretics	-0.30	0.09	0.038
Excluded variables			
Left ventricular ejection fraction	-0.11	0.01	0.479
Daily physical activity time	0.17	0.03	0.252
Calcium antagonists	-0.20	0.04	0.179
CAD patients			
Model I	0.35	0.12	0.010
Included variable			
Physical activity at high intensity	0.35	0.12	0.010
Excluded variable			
Depression score	-0.26	0.07	0.058

HRR₆₀, heart rate recovery 60 s after cessation of exercise; CAD, coronary artery disease; T2D, type 2 diabetes; HDL, high-density lipoprotein.

diabetes, and that this was more closely related to reduced physical activity, low exercise capacity and obesity than to the duration or metabolic features of T2D, including glucose control, or its microvascular or macrovascular complications. In fact, there were no significant differences in autonomic function, as assessed by HR recovery, between the patients with and without T2D after adjustment for physical activity, exercise capacity and obesity.

An association between HR recovery and exercise capacity has also been demonstrated in a few previous studies (Carnethon et al., 2003; Fang et al., 2005). Carnethon et al. (Carnethon et al., 2003) found that poor physical fitness was associated with reduced HR recovery in healthy subjects and that there was an increased risk of developing diabetes among subjects with poor physical fitness and abnormally slow HR recovery compared to those with faster HR recovery. Fang et al. (Fang et al., 2005) also showed that patients with diabetes, who had abnormal HR recovery 1 minute after peak exercise, had a lower exercise capacity than their counterparts with normal HR recovery.

Not only exercise capacity and physical fitness but also physical activity and exercise training may have a positive influence on HR recovery (Carnethon et al., 2005; Buchheit and Gindre, 2006), to the extent that HR recovery appears to be more closely associated with training load than with cardiorespiratory fitness (Buchheit and Gindre, 2006). We observed here that the daily physical activity time was a stronger predictor of HR recovery than exercise capacity when those two variables were included in the same model without any other confounding variables. A previous study with subjects without diabetes showed that self-reported physical activity participation is associated with faster HR recovery (Carnethon et al., 2005), so that participants who reported a high total physical activity had significantly faster HR recovery than those with reduced physical activity. It is well known, however, that self-report questionnaires on physical activity suffer from reporting bias, tending to overestimate physical activity levels (Troiano et al., 2008; Boon et al., 2010). In the present case we used an accelerometer integrated into a wrist-watch, which made it possible to measure physical activity time objectively at as many as five intensity levels, which gives more accurate and objective information on the subjects' daily physical activity. Thus the present data support the concept that the autonomic dysfunction observed in patients with T2D is related low daily physical activity in these individuals.

HR recovery after exercise is associated with age (Cole et al., 1999; Fang et al., 2005), the older patients recovering more slowly after exercise than their younger counterparts, as was also observed in here among the patients with T2D. In addition to the expected correlation between HR recovery and age, we found a positive correlation between HR recovery and HDL cholesterol in the patients with T2D. This cholesterol level is known to be influenced by physical activity (Kokkinos and Fernhall, 1999), and it is obvious that the association between HR recovery and HDL cholesterol must also be related to differences in physical activity. The fact that depression was similarly related to HR recovery in the patients without diabetes is in agreement with a previous report (Hughes et al., 2006) showing that depressive symptoms are associated with cardiovascular autonomic nervous system dysfunction, and that patients with higher depression scores exhibit slower HR recovery after exercise. Finally, the use of calcium antagonists and diuretics was associated with blunted HR recovery in the patients with T2D. This may reflect the fact that the patients taking these drugs had had a history of long-standing hypertension that has not been properly controlled by beta-blocking medication. Hypertension itself has previously been shown to result in cardiovascular autonomic dysfunction (Huikuri et al., 1996).

Fasting plasma glucose, HbA1c and the duration of diabetes have been shown to be closely related to cardiovascular autonomic function and HR recovery (Singh et al., 2000; Cheng et al., 2003; Fang et al., 2005), but contrary to previous studies, we did not find any

correlation between HR recovery and the HbA1c level or the duration of T2D in our patients with diabetes, suggesting that there are also other important determinants of autonomic function in patients with T2D. It is necessary, however, to bear in mind that the present patients had relatively well controlled glycemic state and that only a few of them had abnormal HR recovery according to the criteria used in a previous prognostic study by Georgoulis et al. (2009).

Cardiovascular autonomic dysfunction, as assessed by HR recovery, is closely related to cardiac morbidity and all-cause mortality (Cole et al., 1999; Nissinen et al., 2003; Jouven et al., 2005; Chacko et al., 2008; Georgoulis et al., 2009), which may indicate that reduced HR recovery can be explained by the presence and/or extent of previous myocardial infarction, severity of CAD, and abnormalities in echocardiographic structure and/or function, for instance. HR recovery 1 min after cessation of exercise did not correlate well with any of these factors in either the present patients with or without T2D, however. Moreover, there was unexpectedly a negative correlation between HR recovery and left ventricular ejection fraction in the patients with the diabetes, which was no more evident in multivariate analysis. No correlations were found between HR recovery and other echocardiographic parameters, including left ventricular size, diastolic function and mass. Lack of correlation between HR recovery and left ventricular structure and function has also been documented by Nonaka et al. (2007). These findings suggest that HR recovery is more likely to be influenced by daily exercise habits and obesity, rather than the presence of previous myocardial infarction, severity of CAD, or abnormalities in cardiac function.

4.1. Limitations

The present measurements were performed under continued prescribed medication, for ethical reasons and because of the well-known withdrawal effect of beta-blocker cessation. It is also clear, however, that the results will have more practical implications if the analyses are performed at a time when the patients are on their normal medication. Secondly, the analyses are based on the baseline measurements used in the ARTEMIS exercise study, and therefore the patients with T2D are partly selected and may not be representative of the whole population with diabetes. Typically, patients with T2D who have significant obesity and very low exercise capacity, for example, or with other serious co-morbidities, are not able or willing to participate in exercise interventions, so that such patients are not included in the present analyses. The results should therefore be confirmed in larger, unselected patient samples. Since the present analysis is concerned with baseline data in ARTEMIS exercise study, we can investigate only cross-sectional associations between HR recovery and potential predictors and not longitudinal ones. Previous studies have shown that regular physical activity and exercise improves HR recovery (Carnethon et al., 2005; Soleimani et al., 2010; Jolly et al., 2011). During a 7-year follow-up period, HR recovery declined less among the subjects whose physical activity increased or remained stable, than in those whose physical activity decreased (Carnethon et al., 2005). On the other hand, men with diabetes and CAD achieved less improvement in HR recovery after cardiac rehabilitation than their counterparts without diabetes (Soleimani et al., 2010). This may indicate that the differences in HR recovery between our patients with and without T2D may even increase during the following 2 years of exercise intervention. In any case, it would be interesting to clarify the effect of increasing the physical activity level on changes in HR recovery after exercise intervention.

4.2. Conclusions

Cardiovascular autonomic dysfunction, assessed in terms of reduced HR recovery immediately after exercise, was more common among CAD patients with T2D than in those without T2D. This

impaired HR recovery is more closely related to reduced exercise capacity and daily physical activity, which is a potentially modifiable life-style factor, rather than to either the duration or the severity of the T2D itself, or to any co-morbidities associated with it.

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