Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Recovery of rate-pressure product and cardiac mortality in coronary artery disease patients with type 2 diabetes

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ARTICLE INFO

Article history:
Received 28 August 2018
Accepted 5 March 2019
Available online 11 March 2019

Keywords:
Exercise testing
Ischemic heart disease
Autonomic nervous system
Sudden cardiac death

ABSTRACT

Aims: To investigate prognostic significance of post-exercise recovery of rate-pressure product (RPP) in patients with stable coronary artery disease (CAD) and type 2 diabetes (T2D).
Methods: Patients with angiographically documented CAD and T2D (n = 697) underwent symptom-limited bicycle exercise test. Exercise capacity (EC), heart rate, blood pressure and RPP responses to peak exercise and recovery (2′ and 5′ after cessation of exercise) were analyzed. Cardiac death was the primary and sudden cardiac death (SCD) secondary endpoint.
Results: During a median follow-up of 76 months, 49 cardiac deaths (7.0%) and 28 SCDs (4.0%) were observed. The recovery of RPP at 5′ was the strongest univariate predictor of cardiac death (hazard ratio [HR]: 2.55 per SD decrease, 95%CI: 1.82–3.58, $p < 0.001$) and SCD (HR: 2.34, 95%CI: 1.51–3.62, $p < 0.001$). In multivariate analysis, it remained significantly associated to cardiac death and SCD without (HR: 1.66, 95%CI: 1.14–2.41, $p < 0.01$ and HR: 1.75, 95%CI: 1.08–2.85, $p < 0.05$, respectively) and with additional adjustment for EC and peak RPP (HR: 1.45, 95%CI: 1.09–1.92, $p < 0.05$ and HR: 1.52, 95%CI: 1.01–2.27, $p < 0.05$, respectively).
Conclusions: The recovery of RPP after exercise is a potent predictor of cardiac death in patients with CAD and T2D. It provides significant prognostic information beyond EC and peak RPP.

1. Introduction

Rate-pressure product (RPP) is a widely used method to quantify cardiac workload and hemodynamic response exercise. Peak RPP response to exercise test provides important prognostic information in patients with coronary artery disease (CAD) [1–6]. Depressed hemodynamic response to exercise is common feature in type 2 diabetes (T2D) [7,8]. Predictive value of RPP response to exercise has been reported in patients with diabetes and known or suspected CAD, albeit not independently of other factors [9]. Delayed heart rate (HR) recovery (HRR) is associated with impaired prognosis in

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https://doi.org/10.1016/j.diabres.2019.03.007
0168-8227/

patients with CAD [10–12] and T2D [13,14]. Also, high systolic blood pressure (SBP) during recovery has been associated with risk for cardiovascular morbidities without assessment of the SBP change during recovery in these studies [15–17]. Among patients referred to exercise testing, SBP recovery/peak –ratio was a potent predictor of death but not independently of HRR [18]. It is plausible to expect that RPP recovery would illustrate the combined cardiovascular and autonomic responses and also integrate prognostic significance observed with HRR and SBP recovery. Surprisingly, only Nieminen et al. have reported the outperforming independent prognostic capability of RPP recovery over peak RPP [19]. Yet, the prognostic significance of RPP recovery in patients with stable CAD has remained to be established, particularly among CAD patients with T2D having greater mortality risk and impaired autonomic function [14,20]. The present study was designed to test the hypothesis that delayed RPP recovery would independently be associated with cardiac mortality and sudden cardiac death (SCD).

2. Materials and methods

2.1. Subjects

The study population comprised of CAD patients with T2D from the ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection, ClinicalTrials.gov identifier: NCT01426685) study database collected in the Division of Cardiology of the Oulu University Hospital (Oulu, Finland) between August 2007 and June 2014.[14,20] The ARTEMIS study aims to assess several traditional and novel cardiovascular risk markers as determinants of risk for SCD during 5-year follow-up of patients with stable CAD and T2D. The patients were recruited from a consecutive series of patients with (n = 834) and without T2D (n = 1112) who had undergone coronary angiography 3–6 months earlier and had >3 months from possible previous acute coronary syndrome and revascularization before enrollment and left ventricular (LV) ejection fraction (LVEF) > 35%. Exclusion criteria are described elsewhere in details [14,20]. The patients with contraindication for exercise test or technical problems during the exercise test were excluded from the present study. Therefore, the final sample included 697 CAD patients with T2D (Table 1). Supplementary analyses were performed for 1089 CAD patients without T2D. The study was conducted according to the Declaration of Helsinki, and the local committee of research ethics of the Northern Ostrobothnia Hospital District approved the protocol, and all the subjects gave written informed consent.

2.2. Exercise testing

An incremental symptom-limited maximal exercise test on a bicycle ergometer 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. The patients moved to a supine position within 30 s after cessation of exercise without cool-down period. Supine resting, maximal, peak exercise and recovery (2 and 5 min post-exercise) HRs (15-lead ECG, GE Healthcare, CAM-14, Freiburg, Germany) and BPs (Dinamap Procare 100, GE Medical Systems, Milwaukee, WI) were obtained. From resting ECG, QRS duration, QT interval, QTc interval, Q wave and ECG-based left ventricular hypertrophy were additionally analyzed by custom-made software [21]. EC was calculated as metabolic equivalents (METs) from the mean workload during the last minute of the test. Predicted EC ($EC_{Predicted} = 18 - [0.15 \cdot age]$ for men, $EC_{Predicted} = 14.7 - [0.13 \cdot age]$ for women) was used to obtain age- and sex-specific reference values for the calculation of relative EC ($EC\% = 100 \cdot EC \cdot EC^{-1}_{Predicted}$).[22] Predicted EC was based on large database of treadmill tests [22] that result approximately in ~1 MET larger EC than bicycle ergometer [23]. In the calculation of relative EC, it was assumed that the effects of age and sex on EC are similar regardless of the mode of exercise. Age-adjusted (% of 220 – age) maximal HR and chronotropic response index ($CRI = 100 \cdot (\text{maximal HR} - \text{resting HR}) \cdot (220 - \text{age} - \text{resting HR})^{-1}$) were calculated. HRR was analyzed by subtracting the post-exercise HR from the HR at peak exercise. Similarly, SBP and RPP (=HR · SBP) responses to exercise (peak – resting) and recovery (peak – recovery) were calculated. Additionally, RPP recovery was normalized to peak RPP (RPP recovery [%] = 100 · RPP recovery · peak RPP^{-1}). The incidence of angina pectoris and the level of ST-segment were also registered. Maximal T-wave alternans was detected during the exercise and recovery using modified moving average method described elsewhere in details [24].

2.3. Other measurements

All laboratory measurements and exercise tests were done after 12-hour overnight fast and the patients were instructed to avoid smoking before the tests. Venous blood samples and urine samples were obtained for the analysis of renal function, blood lipids, plasma glucose, and glycated haemoglobin levels. Those subjects without history of diabetes underwent an oral glucose tolerance test to establish their glucose metabolism status. Two-dimensional, M-mode and tissue Doppler echocardiography was performed utilizing the same ultrasound machine for all of the patients (Vivid 7, GE Healthcare, Wauwatosa, WI). LV mass index and LVEF were measured by the biplane method from 2- and 4-chamber views. The patients filled in a health questionnaire containing a question about the frequency of habitual leisure-time physical activity (LTPA). Four LTPA groups were formed by modifying a scale originally developed by Saltin and Grimby: (1) no LTPA (hardly any physical activity or only light housework; (2) LTPA irregularly (some light physical activity randomly, e.g., walking or cycling); (3) moderate-intensity LTPA regularly two to three times weekly; and 4) moderate- or high-intensity LTPA more than three times weekly, where “time”means a period of 30 min [25].

2.4. Follow-up and end-points

End-points were determined from emergency rescue reports, hospital and physician records, autopsy data, death certificates, and interviews with next of kin. The cause and mode of death was reviewed and adjudicated by two independent

Table 1 – Characteristics of patients with coronary disease and type 2 diabetes according to specific endpoint-groups.

Variable	Survivors n = 605	Cardiac death n = 49	Non-cardiac death n = 43
Age (years)	66 (8)	71 (7)‡	73 (8)‡
Men	424 (70%)	41 (84%)*	39 (91%)*
Body mass index (kg/m^2)	29.9 (4.6)	28.7 (4.7)	29.1 (5.0)
Resting heart rate (bpm)	64 (10)	65 (11)	65 (11)
Resting systolic blood pressure (mmHg)	148 (24)	143 (24)	143 (25)
Resting diastolic blood pressure (mmHg)	81 (12)	80 (11)	74 (12)‡§
Smokers	51 (9%)	3 (6%)	3 (7%)
Leisure-time physical activity Inactive	72 (12%)	16 (33%)*	7 (16%)
Irregularly active	254 (42%)	17 (35%)	20 (47%)
Active	198 (33%)	11 (22%)	10 (23%)
Highly active	81 (13%)	5 (10%)	6 (14%)
History of acute myocardial infarction	275 (46%)	30 (61%)	17 (40%)
History of revascularization	485 (81%)	40 (82%)	36 (84%)
CCS class 1	324 (54%)	16 (33%)*	20 (47%)
2	225 (37%)	22 (45%)	17 (40%)
3	56 (9%)	11 (22%)*	6 (14%)
Post-operation syntax score	1 (0–5)	5 (0–16)†	2 (0–8)
Duration of diabetes (months)	62 (24–138)	96 (24–234)	126 (21–276)
Medication			
Beta-blockers	551 (91%)	46 (94%)	40 (93%)
Angiotensin converting enzyme inhibitors or receptor II blockers	474 (79%)	32 (85%)	34 (79%)
Calcium channel blockers	198 (33%)	14 (29%)	15 (35%)
Diuretics	268 (44%)	29 (59%)	24 (56%)
Anticholesterol agents	558 (92%)	39 (80%)*	39 (91%)
Antihyperglycemic agents	462 (76%)	32 (65%)	30 (70%)
Insulin	149 (25%)	24 (49%)*	13 (31%)
Echogardiography			
Left ventricular ejection fraction (%)	64 (9)	57 (15)‡	65 (10)¶
Left ventricular mass index (g/m^2)	108 (27)	126 (31)‡	117 (29)
Laboratory markers			
Glycated haemoglobin (%)	6.9 (1.1)	7.4 (1.8)†	7.4 (1.7)*
(mmol/mol)	52 (12)	58 (21)†	58 (19)*
Glucose (mmol/L)	7.43 (1.83)	8.61 (3.66)†	8.35 (3.28)*
Total cholesterol (mmol/L)	3.85 (0.81)	4.27 (1.12)*	3.61 (0.80)¶
(mg/dL)	149 (31)	165 (43)	140 (31)
LDL cholesterol (mmol/L)	2.19 (0.70)	2.49 (0.90)*	2.03 (0.69)‖
(mg/dL)	85 (27)	96 (35)	78 (27)
HDL cholesterol (mmol/L)	1.19 (0.29)	1.16 (0.35)	1.12 (0.25)
(mg/dL)	46 (11)	45 (14)	43 (10)
Triglycerides (mmol/L)	1.38 (1.00–1.91)	1.42 (1.01–2.21)	1.31 (1.07–1.82)
(mg/dL)	122 (89–169)	126 (89–196)	116 (95–161)
Estimated glomerular filtration rate (mL/min)	105 (40)	81 (35)‡	88 (33)*
Albumin/creatinine-ratio	1.0 (0.6–1.8)	1.5 (1.0–2.8)†	1.7 (0.8–8.2)†
Resting electrocardiography			
QRS duration (ms)	102 (17)	108 (18)	113 (27)†
QRS duration >110 ms	121 (20%)	14 (29%)	14 (33%)
QT interval (ms)	419 (35)	428 (36)	431 (32)
QTc interval (ms)	427 (27)	440 (28)†	444 (32)‡
QTc interval >440/460 ms (♀/♂)	124 (21%)	18 (37%)*	20 (47%)*
Q wave	102 (17%)	14 (29%)	7 (16%)
ECG-based left ventricular hypertrophy	53 (9%)	8 (16%)	2 (5%)
Exercise test			
ST-depression >0.1 mV or angina	270 (45%)	24 (49%)	14 (33%)
>0.2 mV or angina	73 (12%)	7 (14%)	6 (14%)
T wave alternans (μV) Exercise + Recovery	42 (22)	47 (25)	43 (18)
Exercise	39 (22)	44 (25)	41 (20)
Recovery	24 (14)	27 (15)	25 (12)
Exercise capacity (METs)	5.6 (1.5)	4.7 (1.4)‡	4.8 (1.5)†
(%)	76 (18)	68 (21)*	70 (20)

Table 1 – (*continued*)

Variable	Survivors n = 605	Cardiac death n = 49	Non-cardiac death n = 43
Heart rate (bpm) Peak	123 (22)	110 (21)‡	111 (20)†
(%)	80 (13)	74 (13)†	75 (12)
Reserve	59 (21)	45 (18)‡	46 (18)‡
(%)	67 (24)	54 (22)†	56 (20)*
Recovery 2′	35 (13)	26 (13)‡	26 (12)‡
Recovery 5′	44 (15)	33 (14)‡	35 (15)†
Systolic blood pressure (mmHg) Peak	193 (30)	172 (40)‡	174 (29)‡
Response	50 (30)	30 (36)‡	36 (29)*
Recovery 2′	9 (27)	−3 (23)†	1 (24)
Recovery 5′	31 (32)	6 (35)‡	16 (35)*
Rate-pressure product (bpm·mmHg) Peak	24,133 (6,698)	19,220 (6991)‡	19,481 (5,742)‡
Response	14,956 (6,407)	10,063 (6515)‡	10,567 (5,596)‡
Recovery 2′	7,864 (4,581)	4,634 (4066)‡	5,090 (3,971)‡
Recovery 5′	11,218 (5,714)	6,453 (5655)‡	7,592 (5,565)‡

Values are mean (SD), median (1st-3rd quartile) or n (% within group). *CCS class* Canadian Cardiovascular Society grading of angina pectoris, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein. */†/‡ $p < 0.05/0.01/0.001$ compared to survivors, §/‖/¶ $p < 0.05/0.01/0.001$ compared to patients with cardiac death.

investigators; and, if needed, disagreement or uncertainty was resolved in consultation with the investigators (MJJ, HVH). The primary end-point in this study was cardiac death or resuscitation from sudden cardiac arrest, whichever occurred first. SCD, including resuscitations from sudden cardiac arrests, was defined as secondary end-point. The death was defined SCD if it was witnessed and occurred within 1 h of the onset of symptoms or, in case of unwitnessed death, if patient was seen alive and stable 24 h prior to discovery.

2.5. *Statistical analyses*

The between-group differences were assessed by one-way analysis of variance, Kruskal-Wallis or chi-square followed by post hoc analyses by Bonferroni, Mann-Whitney *U* test or chi-square adjusted for multiple comparisons when applicable. Linear regression with collinearity statistics was performed when applicable. The predictive powers of the risk markers were assessed by univariate Cox regression followed by adjustment for established risk markers (age, sex, CCS class, LTPA, glycated haemoglobin, LVEF). In the complementary analyses, EC and peak RPP were also included as covariates. The hazard ratios are presented as risk per standard deviation (SD) decrease with 95% CI. Interactions of exercise variables (divided into 3 groups by; < mean − 1 SD, mean ± 1SD and ≥ mean + 1 SD) with sex were also studied by Cox regression. Competing risks survival analyses were also conducted using approaches of cardiac death vs. non-cardiac death and SCD vs. other cause of death. The discrimination abilities of the exercise test variables were assessed by the C-index and the integrated discrimination index (IDI). Continuous net reclassification index (NRI) was also analyzed based on the individual predicted risks by multivariate Cox regression. Kaplan-Meier analysis was used to illustrate survival curves of different groups of risk. The data were analyzed using SPSS software (IBM SPSS Statistics 21, IBM Corp., New York, USA) and R Statistics (3.3.1, The R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered as statistically significant.

3. Results

During the median follow-up of 76 months (in survivors; 1st-3rd quartile: 58–96 months), there were 49 cardiac deaths (7.0%), 43 non-cardiac deaths (6.2%) and 28 SCDs (4.0%). All the exercise test variables were significantly associated with cardiac death and SCD in univariate Cox regression, except EC for SCD (Table 2). One SD lower RPP_{Peak} involved 124% and 105% higher risk for cardiac death and SCD, respectively, whereas corresponding values with $RPP_{Recovery5'}$ were 155% and 134% (Table 2, Fig. 1). After adjustment for potential confounders, only $HR_{Recovery5'}$, $SBP_{Recovery5'}$ and $RPP_{Recovery5'}$ were associated with cardiac death and SCD (Table 2), the $RPP_{Recovery5'}$ being the most significant and involved 66% and 75% higher risk per 1 SD decrease in $RPP_{Recovery5'}$ for cardiac death and SCD, respectively. With additional adjustment for EC, $RPP_{Recovery5'}$ remained significant factor underlying risk for cardiac death (hazard ratio: 1.61, 95%CI: 1.10–2.38, p = 0.015) and SCD (hazard ratio: 1.89, 95%CI: 1.13–3.13, p = 0.014). No significant interactions with sex were observed.

Neither exercise ST-depression/occurrence of angina nor T-wave alternans were associated with the outcomes (Table 1). The resting QRS duration >110 ms was not associated to cardiac death (hazard ratio: 1.56, 95%CI: 0.84–2.89, p = 0.162) but did so for SCD (hazard ratio: 2.91, 95%CI: 1.37–6.15, p = 0.005) in univariate analysis. However, it did not remain significant predictor of SCD after adjustments (hazard ratio: 1.36, 95% CI: 0.59–3.17, p = 0.474). The abnormal QTc interval was associated with cardiac death (hazard ratio: 2.21, 95%CI: 1.24–3.96, p = 0.007) and SCD (hazard ratio: 3.23, 95%CI: 1.54–6.81, p = 0.002) but did not remain significant after adjustments (hazard ratio: 1.05, 95%CI: 0.55–2.00, p = 0.890 for cardiac death and hazard ratio: 1.47, 95%CI: 0.63–3.43, p = 0.374 for SCD).

$RPP_{Recovery5'}$ correlated significantly with RPP_{Peak} (r = 0.903, p < 0.001) and had significant collinearity (variance inflation factor [VIF] = 5.4). Normalization of $RPP_{Recovery5'}$ to RPP_{Peak} decreased correlation (r = 0.651, p < 0.001) and collinearity to acceptable level (VIF = 1.7) between $RPP_{Recovery5'}$ and RPP_{Peak}.

Table 2 – Predictive value of exercise test variables in patients with coronary artery disease and type 2 diabetes.

	Univariate		Multivariate	
	Cardiac death (n = 49) Hazard ratio per + 1 SD (95%CI)	Sudden cardiac death (n = 28) Hazard ratio per + 1 SD (95%CI)	Cardiac death (n = 49) Hazard ratio per + 1 SD (95%CI)	Sudden cardiac death (n = 28) Hazard ratio per + 1 SD (95%CI)
Exercise capacity (%)	1.57 (1.15–2.15)†	1.41 (0.94–2.10)	1.28 (0.87–1.89)	1.01 (0.60–1.72)
Heart rate				
Peak (%)	1.66 (1.20–2.28)†	1.62 (1.07–2.47)*	1.28 (0.93–1.75)	1.35 (0.88–2.08)
Chronotropic response index (%)	1.96 (1.35–2.84)‡	1.85 (1.34–3.00)*	1.35 (0.94–1.93)	1.41 (0.87–2.31)
Recovery 2′ (bpm)	2.13 (1.53–2.97)‡	1.82 (1.19–2.79)†	1.41 (0.99–2.02)	1.35 (0.86–2.12)
Recovery 5′ (bpm)	2.15 (1.54–3.00)‡	2.03 (1.31–3.14)†	1.44 (1.01–2.06)*	1.54 (0.97–2.47)
Systolic blood pressure				
Peak (mmHg)	1.95 (1.47–2.50)‡	1.88 (1.32–2.68)‡	1.29 (0.97–1.71)	1.38 (0.95–2.02)
Response (mmHg)	1.83 (1.37–2.43)‡	1.81 (1.25–2.64)†	1.28 (0.93–1.77)	1.41 (0.93–2.15)
Recovery 2′ (mmHg)	1.54 (1.17–2.03)†	1.68 (1.18–2.41)†	1.18 (0.87–1.60)	1.40 (0.94–2.08)
Recovery 5′ (mmHg)	1.91 (1.49–2.45)‡	1.83 (1.31–2.55)‡	1.42 (1.07–1.89)*	1.50 (1.02–2.20)*
Rate-pressure product				
Peak (bpm·mmHg)	2.24 (1.61–3.13)‡	2.05 (1.33–3.15)†	1.41 (0.99–2.01)	1.49 (0.94–2.38)
Response (bpm·mmHg)	2.37 (1.68–3.35)‡	2.10 (1.35–3.26)†	1.47 (1.00–2.17)	1.52 (0.93–2.49)
Recovery 2′ (bpm·mmHg)	2.19 (1.58–3.04)‡	2.12 (1.38–3.27)†	1.43 (1.00–2.07)	1.57 (0.99–2.51)
Recovery 5′ (bpm·mmHg)	2.55 (1.82–3.58)‡	2.34 (1.51–3.62)‡	1.66 (1.14–2.41)†	1.75 (1.08–2.85)*

Adjusted for age, sex, Canadian Cardiovascular Society grading of angina pectoris, leisure-time physical activity, glycated haemoglobin, left ventricular ejection fraction.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

In the multivariate Cox regression, relative $RPP_{Recovery5'}$ remained significantly associated to cardiac death (hazard ratio: 1.45, 95%CI: 1.09–1.92, p = 0.011) and SCD (hazard ratio: 1.52, 95%CI: 1.01–2.27, p = 0.045) when also EC and RPP_{Peak} were included as covariates.

$RPP_{Recovery5'}$ was associated with cardiac death regardless of competing risk for non-cardiac death in univariate (hazard ratio: 2.38, 95%CI: 1.69–3.33, p < 0.001) and multivariate analyses (hazard ratio: 1.67, 95%CI: 1.12–2.44, p = 0.011, adjusted also for EC). Similarly, $RPP_{Recovery5'}$ was associated with SCD regardless of competing risk for other types of death in univariate (hazard ratio: 2.17, 95%CI: 1.37–3.45, p < 0.001) and multivariate analyses (hazard ratio: 1.82, 95%CI: 1.11–2.94, p = 0.017, adjusted also for EC).

Addition of $RPP_{Recovery5'}$ to the established model without EC improved discrimination of the patients regarding cardiac death (IDI: 0.032, 95%CI: 0.002–0.077, p = 0.020; C-index from 0.763, 95%CI: 0.678–0.849 to 0.773, 95%CI: 0.691–0.856) and tended to improve classification of the patients (NRI: 0.164, 95%CI: −0.013–0.343, p = 0.086). When EC was included in the established model, the addition of $RPP_{Recovery5'}$ did improve neither discrimination nor classification. For the SCD, the $RPP_{Recovery5'}$ did not improve discrimination (IDI: 0.020, 95%CI: −0.007–0.075, p = 0.100; C-index from 0.676, 95%CI: 0.537–0.814 to 0.714, 95%CI: 0.571–0.858) or classification (NRI: 0.167, 95%CI: −0.108–0.389, p = 0.126).

In the CAD patients without T2D, all exercise test variables, except for SBP $_{Recovery2'}$, were associated with cardiac mortality in the univariate analysis (Table 3). After adjustments for potential confounders, only EC, CRI and $HR_{Recovery2'}$ remained significant factors underlying the risk for cardiac death. The RPP variables were not associated to cardiac death or SCD in the multivariate analysis in CAD patients without T2D.

4. Discussion

The main finding of the present study was that among exercise test variables post-exercise recovery of RPP was the most powerful factor related to the risk for cardiac death and SCD in CAD patients with T2D. Notably, it provided significant prognostic information beyond EC and RPP at peak exercise and outperformed the prognostic significance of standard resting and exercise ECG markers. However, it provided limited improvement in discrimination and reclassification analyses when added to the established risk model.

The present study confirmed our hypothesis that RPP recovery provides significant prognostic value in patients with stable CAD and T2D. It was associated with risk for cardiac death and SCD independently of established risk markers and competing risks for other types of death. Notably, the predictive value of HRR and recovery of SBP and RPP, measured at 5 min post-exercise, turned out to be greater than measures quantifying hemodynamic responses to peak exercise that were not associated with cardiac death or SCD in multivariate analyses. Evidently, prognostic significances of HRR and SBP recovery were combined with RPP recovery. Therefore, as readily available index, RPP recovery is a potent marker for risk stratification in patients with CAD and T2D in clinical practice. However, it yielded borderline improvements

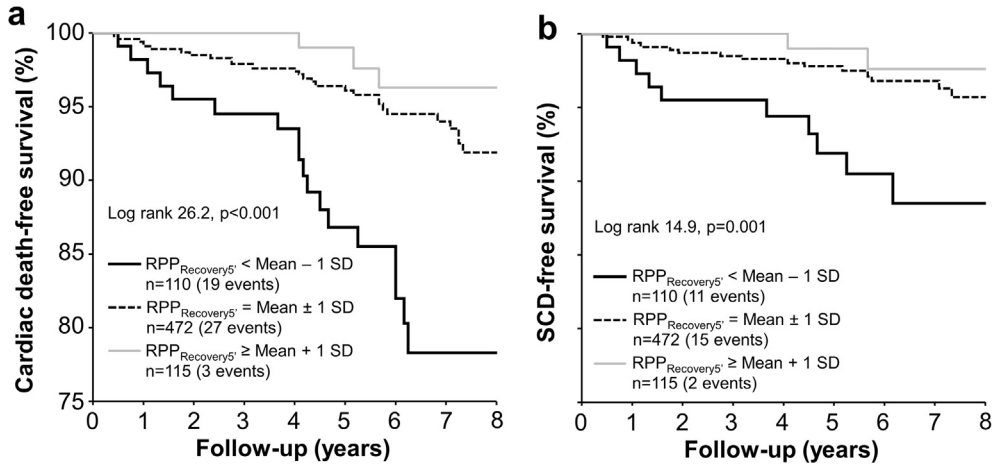

Fig. 1 – Kaplan-Meier survival curves of the groups according to recovery of rate-pressure product ($RPP_{Recovery5'}$) in patients with coronary artery disease and type 2 diabetes.

in discrimination and classification of the patients and that is why confirmatory studies are warranted.

The recovery of RPP, as absolute value, was strongly related to RPP_{Peak} which compromised multivariate analysis with both variables included. Therefore, RPP recovery was also normalized to RPP_{Peak}, which considerably decreased correlation and collinearity between these markers. Subsequently, it was also observed that relative RPP recovery was associated with the outcomes independently of RPP_{Peak} as well as EC. This underscores the greater predictive value of RPP recovery compared to RPP_{Peak} and suggests the importance of post-exercise monitoring of hemodynamics in exercise testing. While prognostic significance of RPP response to peak exercise has been promising in many populations [1–6,26], it has provided limited additional value to EC and HR responses to exercise in patients referred to exercise test and without CAD [27]. Also, in small sample of patients with T2D, RPP response to exercise was not associated with the presence of silent myocardial ischemia independently of EC and HR responses to exercise and recovery [28]. Taken together, RPP recovery might be more potent and independent prognostic marker for cardiac death and SCD in patients with stable CAD and T2D. The latter notion is also supported by the findings by Nieminen et al. among patients referred to exercise testing [19].

Table 3 – Predictive value of exercise test variables in CAD patients without diabetes (n = 1089).

	Univariate		Multivariate	
	Cardiac death (n = 31) Hazard ratio per + 1 SD (95%CI)	Sudden cardiac death (n = 16) Hazard ratio per + 1 SD (95%CI)	Cardiac death (n = 31) Hazard ratio per + 1 SD (95%CI)	Sudden cardiac death (n = 16) Hazard ratio per + 1 SD (95%CI)
Exercise capacity (%)	2.22 (1.47–3.33)‡	2.08 (1.18–3.70)*	1.92 (1.20–3.03)†	3.13 (0.87–3.13)
Heart rate				
Peak (%)	1.96 (1.33–2.86)‡	1.96 (1.18–3.33)†	1.47 (0.99–2.17)	1.67 (0.97–2.86)
Chronotropic response index (%)	2.13 (1.45–3.13)‡	2.08 (1.23–3.57)†	1.54 (1.02–2.33)*	1.79 (1.00–3.23)
Recovery 2′ (bpm)	2.63 (1.96–3.57)‡	1.96 (1.25–3.13)†	2.17 (1.41–3.33)‡	1.75 (0.98–3.13)
Recovery 5′ (bpm)	2.22 (1.54–3.23)‡	2.13 (1.28–3.45)†	1.52 (0.98–2.38)	1.89 (1.02–3.45)*
Systolic blood pressure				
Peak (mmHg)	1.67 (1.19–2.33)†	1.52 (0.94–2.44)	1.20 (0.83–1.75)	2.56 (0.75–2.08)
Response (mmHg)	1.47 (1.06–2.04)*	1.27 (0.79–2.00)	1.03 (0.71–1.49)	1.04 (0.62–1.75)
Recovery 2′ (mmHg)	1.32 (0.92–1.85)	1.16 (0.71–1.92)	0.92 (0.61–1.37)	0.97 (0.57–1.64)
Recovery 5′ (mmHg)	1.72 (1.25–2.38)*	1.73 (1.11–2.70)*	1.16 (0.79–1.69)	1.47 (0.88–2.44)
Rate-pressure product				
Peak (bpm·mmHg)	2.38 (1.59–3.57)‡	2.08 (1.20–3.57)†	1.56 (0.99–2.50)	1.72 (0.93–3.23)
Response (bpm·mmHg)	2.44 (1.61–3.57)‡	2.08 (1.22–3.57)†	1.59 (0.99–2.56)	1.79 (0.93–3.33)
Recovery 2′ (bpm·mmHg)	2.22 (1.52–3.33)‡	1.67 (1.01–2.78)*	1.47 (0.92–2.38)	1.32 (0.71–2.44)
Recovery 5′ (bpm·mmHg)	2.33 (1.56–3.45)‡	2.17 (1.28–3.70)†	1.47 (0.93–2.33)	1.47 (0.93–2.33)

Adjusted for age, sex, Canadian Cardiovascular Society grading of angina pectoris, leisure-time physical activity, glycated haemoglobin, left ventricular ejection fraction.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

Our supplementary analyses in CAD patients without T2D showed significant univariate associations of exercise and recovery variables to cardiac death and SCD. However, only HRR and HR response to exercise predicted outcome in the multivariate analyses. The risk ratios regarding these variables were close to those observed in CAD patients with T2D and the small number of endpoints in CAD patients without T2D most likely explains the lack of significant association of RPP recovery in these sub-analyses. Therefore, it is plausible to consider that exercise and recovery responses in central hemodynamics are significant risk factors in CAD patients regardless of glycemic status.

The main hemodynamic response contributor to exercise and recovery is autonomic nervous system which plays an important part in pathophysiology of cardiac death and SCD [29–32]. Impaired exercise responses in HR and SBP are mostly explained by depressed vagal and augmented sympathetic activity at rest accompanied with modest vagal withdrawal and sympathetic response to exercise that additionally limit the EC [29]. Pain and ischemia may also decrease these responses [33]. During the post-exercise recovery, there is faster vagal reactivation followed by slower sympathetic withdrawal [34]. In the present study, recovery indexes measured at 5 min after exercise were more predictive than those measured at 2 min. Therefore, impaired sympathetic response to recovery may be the main culprit in the present observations. Accumulation of metabolites in active muscle opposes vascular sympathetic responses – a phenomenon called sympatholysis [35]. In turn, sympathetic vasoconstriction persists in inactive muscles. Impaired sympatholysis with persistent vasoconstriction in the inactive muscles may, therefore, delay recovery of blood pressure regardless of cardiac autonomic responses that is opposed also by atrial reflex due to sustained venous return. As impaired sympatholysis has not been verified in T2D, it has been hypothesized that advanced T2D with endothelial dysfunction may alter this mechanism [36] that may well explain the abnormal SBP and, thus, RPP recovery in the high risk CAD patients with T2D.

The present study is partly limited by the small number of endpoints why only the most relevant covariates were allowed to be included in the established model. In turn, the use of continuous risk variables decreases the possibility for overly optimized results. Therefore, confirmatory studies are warranted. The adjudication of SCD, the present secondary endpoint, raises questions about the reliability of the outcome because death certificates have often been considered as unreliable method of adjudication. However, medicolegal autopsy is mandatory according to law in Finland whenever a death has been sudden and unexpected even when the prior cardiac condition is known which increases our confidence in adjudication of SCD.

In conclusion, the recovery of rate-pressure product after exercise is a potent predictor of cardiac death in patients with coronary artery disease and diabetes. It provides significant prognostic information beyond exercise capacity and peak rate-pressure product and is potent candidate for risk stratification in patients with ischemic heart disease and diabetes.

Acknowledgments

The authors gratefully acknowledge the assistance of the registered nurses Pirkko Huikuri, Päivi Koski, Päivi Kastell and Sari Kaarlenkaski. No relationships to disclose.

Funding

This work was supported by Finnish Technology Development Center, TEKES, Helsinki, Finland [grant number n/a, 2007–2014]; the Academy of Finland, Helsinki, Finland [grant number #267435, 2014–2017]; the Sigrid Juselius Foundation, Helsinki, Finland [grant number n/a, 2018], the Finnish Foundation for Cardiovascular Research, Helsinki, Finland [grant number n/a, 2017] and the Paulo Foundation, Espoo, Finland [grant number n/a, 2016]. The authors appreciate the financial support received from the ARTEMIS consortium partners (Polar Electro, Kempele, Finland and Hur Oy, Kokkola, Finland).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.007.

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