

SIGNIFICANCE OF PROGNOSTIC PARAMETERS OF EXERCISE TESTS

PhD Thesis

Tibor Sydó, MD

Doctoral School of Basic and Translational Medicine
Semmelweis University



Supervisor: Béla Merkely MD, DSc

Official reviewers: Csaba Sós MD, PhD, DSc
István Hritz MD, PhD

Head of the Complex Examination Committee:
Zoltán Benyó MD, DSc

Members of the Complex Examination Committee:
József Pucsock, MD, DSc, Gergely Szabó MD, PhD

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INTRODUCTION

Ever since the concept of heart rate (HR) recovery on the exercise test in clinical practice was proposed by Lauer and colleagues in 1999, investigations have consistently demonstrated its ability to identify higher risk patients in mixed cohorts – with and without documented coronary artery disease, in patients referred for nuclear stress testing and possible coronary angiography, and patients with symptomatic coronary artery disease. HR recovery is impaired in patients with obstructive sleep apnea, silent myocardial ischemia, heart failure with preserved ejection fraction, and Type 2 diabetes, though these studies did not report long-term outcomes.

Diabetes is associated with an excess long-term mortality, primarily due to associated cardiovascular diseases. It is frequently associated with autonomic neuropathy, one manifestation of which is an impaired HR response to exercise. Both impaired HR response to exercise and diabetes have been shown to be strong and independent predictors of mortality, but the effect of diabetes on exercise HR and the potential role of impaired HR in mortality in diabetic patients have not been adequately investigated.

The prognostic potential of HR recovery in a primary prevention population without documented coronary artery disease has not been fully examined either. In primary prevention cohort, cardiovascular (CV) deaths may not constitute the majority of all deaths, so it is important to know if non-CV deaths are also related to HR recovery.

Another issue is whether adjusting the HR recovery for different subgroups will improve its performance. Among exercise test prognostic factors, FAC is adjusted for age and sex, while peak exercise HR is adjusted for age and beta blocker use – either ignored in beta-blocked patients or given a different age-adjusted target. It is therefore essential to determine if HR recovery varies by age, sex, and beta blocker use, and whether adjustment for any of these factors improves its performance. These questions represent the focus of the current investigation while also an attempt of validating the prognostic value of HR recovery in a primary prevention cohort. We extended our examination to diabetic patients, and assessed resting HR, peak HR, HR reserve, HR recovery and calculated the chronotropic index (CI) according to diabetes in a large cohort of patients undergoing exercise testing.

OBJECTIVES OF OUR STUDIES

We have had a strong cooperation with Mayo Clinic Cardiovascular Health Clinic, Rochester, USA since 2014. In order to study HR responses to exercise, we assessed the large Mayo Integrated Stress Center Database (MISC). This database contains exercise testing data of almost 140000 patients with more than 200000 exercise tests covering approximately 32 years.

1. Our first aim was to study exercise HR responses in a primary prevention population with a focus of HR recovery
 - to determine if HR recovery varies by age, sex, and beta blocker use, and whether adjustment for any of these factors improves its performance
 - to validate the prognostic value of HR recovery in a primary prevention cohort and determine its long-term prognostic significance.
2. Our second aim was to extend our research to diabetic patients and investigate HR responses to exercise
 - to study the effect of diabetes on exercise HR parameters: resting HR, peak HR, HR reserve, HR recovery and chronotropic index (CI)
 - to investigate the role of impaired HR in excess mortality.

METHODS

This was a retrospective study approved by Mayo Clinic Rochester Institutional Review Board. Subjects not consenting to have their data used in research under Minnesota Statute (§144.335) were excluded.

Participants

Patients who underwent exercise treadmill testing from September 21, 1993 through December 20, 2010 were identified retrospectively using the Mayo Clinic Integrated Stress Center (MISC) database.

Inclusion criteria were as follows: non-imaging stress test, Minnesota resident, symptom-limited treadmill test performed on the Bruce protocol. Minnesota residents were more likely than non-Minnesota residents to have follow-up medical evaluation at Mayo, and their vital status was readily available from the Mayo Clinic records and the Minnesota Death Index. The study cohort was limited to patients aged ≥ 20 years (in an attempt to limit referral bias) and < 90 years, because there were very few extremely elderly patients in the database. For the HR recovery analyses we included only patients between age 30-79 years.

Tests were excluded if the patient (1) had documented history of cardiovascular (CV) disease, including ischemic heart diseases, heart failure, cardiac surgery, structural or valvular heart diseases, major arrhythmias, defibrillator or pacemaker, congenital heart diseases, cerebrovascular diseases, and peripheral vascular diseases; (2) the test was not symptom-limited but stopped because of ST changes, major arrhythmias, or abnormal blood pressure response; (3) active recovery for at least 1 minute was not completed; 4) peak exercise or 1-minute recovery HR were impaired by a paroxysmal arrhythmia. Where multiple qualifying tests were available for a given patient, the first test chronologically was chosen to maximize follow-up.

Clinical Data

Demographic and clinical information were collected prospectively at the time of the stress study. HR and other exercise data were uploaded into the database electronically from the GE CASE stress testing systems (Milwaukee, WI). Patient characteristics including age, sex, anthropometrics, and comorbidities were extracted from patient medical charts and patient interview at the time of the exercise test. We specifically looked for diabetes mellitus (defined by prior diagnosis or receiving glucose-lowering medication), hypertension (defined by prior diagnosis or receiving anti-hypertension medication), obesity (defined as $BMI \geq 30 \text{ kg/m}^2$), past and current smoking. Medication use – beta blockers, calcium channel blockers, aspirin, statins, ACE-inhibitors or angiotensin receptor blockers, and diabetic treatment drugs – oral hypoglycemics and insulin – was available in the database.

Exercise Test Protocol and Variables

Symptom-limited treadmill exercise testing was performed on usual medications using the standard Bruce protocol according to ACC/AHA guidelines. Resting HR and blood pressure (BP) measurements were obtained in the standing position. Symptoms, BP, HR, rating of perceived exertion (RPE), and workload were electronically entered into the database during the final minute of each stage of exercise, peak exercise, 1 and 3 minutes of active recovery at 1.7 MPH/0% grade, and 6 minutes post-peak exercise in seated recovery.

Exercise test interpretation data including reason for termination, symptoms, abnormal signs, and exercise electrocardiographic (ECG) analysis were added to the database immediately after the test. FAC was expressed as $100\% \times \text{actual performance time/predicted performance time}$ based on previous publications from our laboratory. Peak HR was also expressed as percent predicted peak HR. HR reserve was calculated as the difference between peak and resting HR. CI was defined as HR reserve divided by the predicted HR reserve as

previously reported in our laboratory for healthy men and women and defined as abnormal if < 0.8 . HR recovery was calculated as peak exercise HR minus HR at 1 minute of active recovery at 1.7 MPH/0% grade and was considered abnormal if < 13 beats/minute. An abnormal exercise ECG was defined as any ST depression or elevation > 1.0 mm irrespective of the resting ECG, while an abnormal exercise ECG was considered positive only if the resting ECG did not present significant ST-T abnormalities, the patient was not taking digitalis, and rate-related left bundle branch block did not occur.

Mortality Outcomes

Outcomes were taken from Mayo Clinic patient records and the Minnesota Death Index, which was reviewed in September 2014 (Research Aim 2) and March 2016 (Research Aim 1). Follow-up was calculated as the time from the stress test to death (identified by the Minnesota Death Index as last date of vital status). This methodology provides 100% complete follow-up data. For the HR recovery analyses, CV and non-CV deaths were divided. A death was considered to be CV-related if a CV condition was included among the first 3 listed causes in the Minnesota Death Index; otherwise the death was considered non-CV. Mortality data were classified using International Classification of Diseases (ICD) 9 (391, 391.9, 394-398, 402, 404, 410-414, 415-417, 420-429, 430-438, 440-448, 451-454, 456-459) and ICD 10 (I101, I05-I09, I11, I13, I20-I25, I26-I28, I30-I52, I60-69, I70-I79, I80-89) codes.

Statistical Analysis

Patient characteristics, outcomes, and exercise data were analyzed by decade of age. Differences among continuous variables by age group were assessed by the analysis of variance under the general linear model with multiple comparisons handled by Tukey's method, while Pearson's Chi-Squared Test of continuity was used to test age group differences in discrete variables. Statistics were performed using SAS 9.4 (Raleigh, NC). $P < .05$ was considered significant for all analyses.

- ***Research Aim 1***

Similar to a previous paper on peak HR by age and sex from our laboratory (33), the first step in the analysis was to determine factors that significantly affect HR recovery using stepwise multivariate regression, then to create a “pure cohort” by eliminating patients with those factors. This allowed us to identify the true physiologic change in HR recovery with age and sex. The next step in the analysis was to determine if the standard definition of abnormal HR recovery of < 13 bpm would predict the outcomes of total death, CV death, and non-CV death in this primary prevention dataset using the whole cohort. Cox Proportional Hazards Regression was employed for this analysis. Further analyses were stratified by age, sex, FAC, presence of hypertension, diabetes, current smoking and use of a HR-lowering drug. Differences in Hazard ratios between different strata were determined by the Z-score method.

- ***Research Aim 2***

Multivariable linear regression analysis was used to identify the effects of diabetes on HR adjusted for age, sex, and HR-lowering drugs then in a larger model including current smoking, hypertension, abnormal exercise ECG and type of diabetic treatment. For the simple model we chose factors that have a well-established effect on HR variables (33), while the full model is more exploratory. We determined the effect of exercise HR responses on total mortality in diabetics and non-diabetics using by Cox hazard regression first in the simple adjustment model and then in the extended adjustment model, as described above. We also performed Cox regression to compared mortality according to 0, 1, or 2 of the exercise HR abnormalities (abnormal HR recovery and abnormal CI) in both diabetic and non-diabetic patients.

RESULTS

Study Population

A total of 19,551 patients were available for the HR recovery analysis. Their demographic and clinical data, stratified by decade of age, are provided in Table 1, along with the long-term outcome data – shown below in Table 1 for convenience.

Table 1. Baseline characteristics and outcomes in the five age groups for the full clinical cohort.

	Age: 30-39 N = 2664	Age: 40-49 N = 6703	Age: 50-59 N = 6047	Age: 60-69 N = 3112	Age 70-79 N = 1025	P
Age (years)	35.7 ± 2.8 ¹	44.7 ± 2.8 ²	54.0 ± 2.9 ³	63.9 ± 2.8 ⁴	73.0 ± 2.6 ⁵	< .0001
Female	810 (30.4) ¹	2170 (32.4) ¹	2097 (34.7) ²	2171 (40.8) ³	408 (39.8) ³	< .0001
BMI (kg/m²)	29.2 ± 6.3 ³	28.8 ± 5.1 ²	28.8 ± 5.1 ²	28.4 ± 4.7 ²	27.2 ± 4.0 ¹	< .0001
Hypertension	285 (10.7) ¹	1000 (14.9) ²	1492 (24.7) ³	1059 (34.0) ⁴	444 (43.3) ⁵	< .0001
Diabetes	83 (3.1) ¹	273 (4.1) ¹	382 (6.3) ²	248 (8.0) ³	95 (9.3) ³	< .0001
Current smoker	416 (16.2) ⁴	892 (13.7) ³	633 (10.8) ²	196 (6.6) ¹	53 (5.3) ¹	< .0001
Obesity	1046 (39.3) ⁴	2410 (36.0) ^{2,3}	2259 (37.4) ^{3,4}	1072 (34.4) ²	255 (24.9) ¹	< .0001
Poor CRF	866 (32.5) ⁴	1532 (21.4) ^{1,2}	1245 (20.6) ¹	724 (23.3) ^{2,3}	278 (27.1) ³	< .0001
Deaths	40 (1.5) ¹	158 (2.4) ¹	287 (4.8) ²	437 (14.0) ³	350 (34.2) ⁴	< .0001
CV death	11 (0.4) ¹	50 (0.8) ¹	69 (1.1) ¹	133 (4.3) ²	142 (13.8) ³	< .0001
Non-CV death	29 (1.1) ¹	108 (1.6) ¹	218 (3.6) ²	304 (9.8) ³	208 (20.3) ⁴	< .0001

Continuous data are presented mean ± SD; categorical data as N (percentage of sample).

BMI = body mass index, CRF = cardiorespiratory fitness, CV = cardiovascular

Poor cardiorespiratory fitness defined as functional aerobic capacity (FAC) < 80% predicted for age and sex on exercise test.

Different superscripts indicate a statistically significant difference between age groups. Superscript = 1 is arbitrarily set at the lowest value for each variable.

Diabetes and hypertension rates increased progressively with age, while obesity and current smoking showed an opposite trend. Not surprisingly, there were relatively more women in the older age groups. Poor cardiorespiratory fitness (CRF) – identified by an FAC <

80% – was highest in the youngest age group, likely reflecting referral bias in younger patients.

For our diabetes project we initially identified 101544 exercise tests over the study period to identify 21,396 patients meeting study criteria. Reasons for exercise testing included symptoms in 42% (predominantly chest pain, 31%) and referral to preventive cardiology for exercise prescription in the remaining 58%. Of these patients, 1200 had diabetes (5.4%), predominately type 2 diabetes; type 1 diabetics represented a small portion of the diabetic patients (N = 137, 11.4%). Clinical characteristics of the patients are presented according to the presence of diabetes in **Table 2** (dissertation). Approximately 90% were Caucasian, 3% African American, 7% other race. In general, the cardiovascular risk factor burden was low, consistent with the higher socio-demographic characteristics of the cohort and the exclusion of baseline cardiovascular disease. Among the diabetic patients, 352 (29%) were on insulin therapy, 625 (52%) were on oral hypoglycemic drugs, and 69 (6%) on both.

Exercise Test Results

Table 3 in the dissertation provides the exercise test data for the full clinical cohort of 19,551 patients. Because of the large sample size, even minor differences, such as in resting HR or highest rating of perceived exertion reached statistical significance, though some age trends were pronounced, such as the well-documented trend towards decreasing peak exercise HR with age. HR recovery also declined significantly with age, while the proportion of patients with HR recovery < 13 bpm increased significantly. Not surprisingly, the portion of patients taking HR-lowering drugs increased significantly with age. The frequency of both positive and all abnormal exercise ECGs also increased steadily with age.

Factors Affecting Heart Rate Recovery

For the next step in the analysis, stepwise multivariate regression to determine factors significantly affecting HR recovery was performed (**Table 4**.)

Table 4. Multivariate regression analysis to determine factors affecting HR recovery.

Variable	Parameter Estimate	Standard Error	Partial R ²	Model R ²	F	P-value
Intercept	31.79	0.29			12107.3	<.0001
Age	-0.21	0.0055	0.071	0.071	1445.6	<.0001
Poor CRF	-3.92	0.14	0.063	0.134	1368.1	<.0001
Obesity	-1.32	0.12	0.0060	0.140	132.5	<.0001
Current smoking	-1.90	0.18	0.0051	0.145	113.2	<.0001
Hypertension	-1.08	0.15	0.0027	0.148	60.9	<.0001
Diabetes	-1.46	0.25	0.0016	0.149	35.8	<.0001

CRF = cardiorespiratory fitness

The N for **Table 4** was 18887, as 664 patients (3.4%) had one missing covariate, principally smoking status. Intercept and age were highly significant in the regression, and 5 other factors – poor CRF, obesity, current smoking, hypertension, and diabetes – all showed significant (negative) effects on HR recovery, whereas sex, taking a HR-lowering drug, and an abnormal exercise ECG did not affect HR recovery significantly. Only age and poor CRF contributed more than 1% to the model R². Based on these results, we formed our pure cohort by eliminating patients with the 6 HR recovery-lowering factors, leaving us 7852 patients.

Heart Rate Recovery in Age Groups

Table 5 shows means, medians, and interquartile range for HR recovery, and percent of patients with HR recovery less than the traditional cut-point of 13 bpm in the first minute of active recovery according to decade of age in the pure cohort.

Table 5. Heart rate recovery distribution in the pure cohort.

	Age: 30-39 N = 1056	Age: 40-49 N = 2967	Age: 50-59 N = 2390	Age: 60-69 N = 1116	Age 70-79 N = 323	P
Resting HR (bpm)	76.1 ± 12.7 ²	74.8 ± 12.4 ¹	74.6 ± 12.1 ¹	75.1 ± 12.1 ^{1,2}	73.8 ± 11.1 ¹	<.001
Peak exercise HR (bpm)	182.4 ± 11.4 ⁵	176.4 ± 11.9 ⁴	168.6 ± 12.9 ³	159.1 ± 13.7 ²	149.4 ± 14.6 ¹	<.001
Female (%)	327 (31.0) ¹	990 (33.4) ^{1,2}	880 (36.8) ²	509 (45.6) ³	147 (45.5) ³	<.001
HR-lowering drug use (%)	23 (2.2) ^{1,2}	54 (1.8) ¹	60 (2.5) ^{1,2}	43 (3.8) ²	23 (7.1) ³	<.001
Mean HR recovery (bpm)	22.9 ± 8.3 ⁴	22.3 ± 8.2 ⁴	21.1 ± 8.0 ³	18.4 ± 7.4 ²	14.9 ± 7.3 ¹	<.001
Median HR recovery (bpm)	22	22	21	18	14	
Interquartile range (bpm)	17 - 28	17 - 27	16 - 26	13 - 23	10 - 20	
HR recovery < 13 bpm (%)	87 (8.4) ¹	298 (10.0) ¹	311 (13.0) ²	240 (21.5) ³	134 (41.5) ⁴	<.001

Continuous data are presented mean ± SD; categorical data as number (percentage of sample).

HR = heart rate

Pure cohort created by excluding patients with hypertension, diabetes, current smoking, obesity (BMI ≥ 30 kg/m²), and poor cardiorespiratory fitness (functional aerobic capacity < 80% age-sex predicted).

Different superscripts indicate a statistically significant difference between groups. Superscript = 1 is arbitrarily set at the lowest value for each variable.

We propose that these data represent the true effect of age on HR recovery. At each age group, HR recovery in the pure cohort was higher than in the full cohort, as expected. Average HR recovery is relatively constant through ages 30 – 39, while through ages 50 – 59 it begins to decrease more rapidly as age increases. The portion of patients with a HR recovery below the traditional cut point of 13 bpm is only 8.4% at age 30 – 39 but has risen to 41.5% by age 70 – 79.

Outcomes by Abnormal Heart Rate Recovery

There were a total of 1,271 deaths (6.5%) in the full cohort over an average follow-up of 12.4 ± 5.0 years. Consistent with exclusion of baseline CV disease and residence in a state (Minnesota) with overall low CV death rates, there were actually more non-CV deaths (867, 4.4%) than CV deaths (405, 2.1%). Not surprisingly, women were at a lower age-adjusted risk of death (0.70 with 95% confidence interval [0.62 – 0.90]), compared to men.

Using the full clinical cohort, an abnormal HR recovery by the traditional value of < 13 bpm in the first minute post-peak exercise during active recovery was a significant risk factor for death from any cause, CV death, and even non-CV death in this primary prevention cohort. Hazard ratios for an abnormal HR recovery predicting death, CV death and also non-CV death are shown in **Figure 5**.

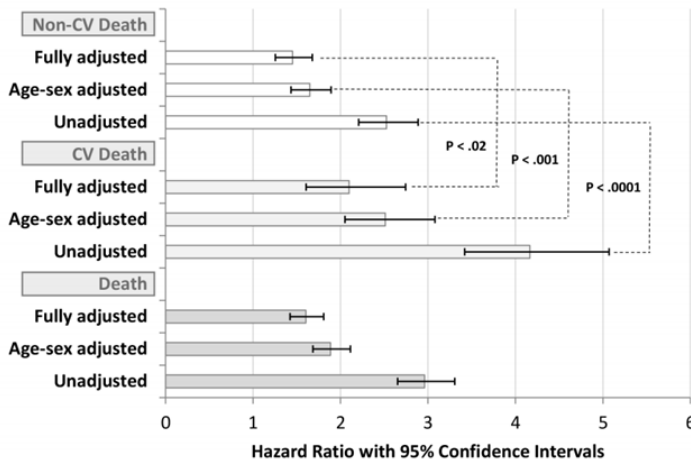


Figure 5. Hazard ratios with 95% confidence intervals for an abnormal heart rate (HR) recovery predicting death, cardiovascular (CV) death, and non-CV death. Three models are shown for each outcome: unadjusted; adjusted for age and sex; fully adjusted for age, sex, diabetes, hypertension, obesity, current smoking, and poor cardiorespiratory fitness. Hazard ratios for CV and non-CV death are compared by the Z-score method.

Three models are shown for each outcome: unadjusted; adjusted for age and sex; and fully adjusted for age, sex, diabetes, hypertension, obesity, current smoking, and poor CRF. The hazard ratios in all models for all outcomes are statistically significant. The hazard ratio for abnormal HR recovery for CV versus non-CV death was significantly higher in the unadjusted (P<.0001), age-sex adjusted models (P<.001), and fully adjusted (P<.02) models. We have therefore demonstrated that an abnormal HR recovery is a significant predictor of death, CV death, and even non-CV death in our primary prevention cohort.

For further analyses, we focused on CV mortality since its association with abnormal HR recovery was strongest. We divided the full cohort according to 3 age groups, 30 – 59 (based on the minimal change in HR recovery across this age range as mentioned above), then 60 – 69, and 70 – 79, as HR recovery declined significantly over these older age groups. Hazard ratios for CV death according to HR recovery in the 3 age groups are shown in Figure 6. Hazard ratios were statistically significant in all age groups and not significantly different amongst the 3 age groups.

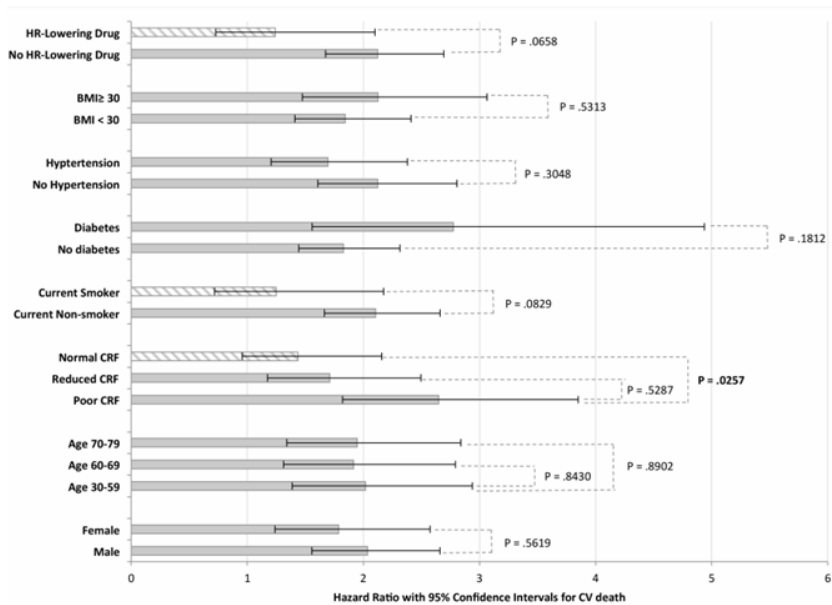


Figure 6. Hazard ratios with 95% confidence intervals for an abnormal heart rate (HR) recovery predicting cardiovascular (CV) death stratified by age, sex, presence of obesity, hypertension, diabetes, current smoking, use of HR-lowering drug, and level of cardiorespiratory fitness (CRF).

Poor CRF refers to functional aerobic capacity (FAC) < 80%, reduced CRF to FAC 80 – 99%, and normal CRF to FAC ≥ 100% predicted. All models are fully adjusted for age, sex, diabetes, hypertension, obesity, current smoking, and poor CRF. Hazard ratios for CV death are compared by the Z-score method.

Hazard ratio bars filled with striped pattern indicate non-significant findings.

Figure 6 also shows the predictive value of abnormal HR recovery according to sex, 3 levels of CRF, smoking status, diabetes, hypertension, obesity, and use of a HR-lowering drug. Abnormal HR recovery significantly predicted outcomes in all sub-groups except current smokers, patients with normal CRF ($\geq 100\%$ FAC), and patients taking a HR-lowering drug; in these sub-groups, the confidence intervals in the Hazard Ratios included 1.0. As noted in the displayed P-values, there was a significant difference in the hazard ratios in poor versus normal CRF, while the differences in hazard ratios according to HR-lowering drug and current smoking were of borderline significance. On the other hand, abnormal HR recovery did not perform differently in males versus females, in reduced versus normal CRF, among the three age groups, or in patients with or without diabetes, hypertension, or obesity.

Exercise Test Results by Diabetes

Exercise test results by diabetics are given in **Table 6**.

	Patients without Diabetes (N = 20196)	Patients with Diabetes (N = 1200)	P-value
Exercise time (min)	9.2 ± 2.5	7.5 ± 2.2	<.001
FAC (%)	96 ± 22	82 ± 22	<.001
Resting HR (beats/minute)	77 ± 13	81 ± 14	<.001
Peak HR (beats/minute)	165 ± 19	154 ± 20	<.001
HR reserve (beats/minute)	88 ± 19	73 ± 19	<.001
HR recovery (beats/minute)^a	19 ± 9	15 ± 8	<.001
HR recovery < 13 beats/minute (%)	4243 (21.0)	463 (38.6)	<.001
Chronotropic Index^b	0.99 ± 0.20	0.86 ± 0.22	<.001
Chronotropic Index < 0.8 (%)	3329 (16.5)	478 (39.8)	<.001
Resting systolic BP (mmHg)	123 ± 18	128 ± 19	<.001
Resting diastolic BP (mmHg)	80 ± 11	78 ± 11	<.001
Peak systolic BP (mmHg)	177 ± 26	184 ± 27	<.001
Peak diastolic BP (mmHg)	77 ± 16	78 ± 16	<.001
Peak RPE	18.1 ± 1.0	18.0 ± 1.0	.06
Positive ECG (%)	923 (4.6)	103 (8.6)	<.001
Abnormal ECG (%)^c	1593 (7.9)	141 (11.8)	<.001

Continuous data are presented mean ± SD, categorical data as percentage of sample.

Abbreviations: BP = Blood Pressure; CI = Chronotropic Index, ECG = electrocardiogram;

FAC = Functional Aerobic Capacity; HR = Heart Rate; RPE = Rating of Perceived Exertion

^a Heart rate recovery was defined as peak HR minus HR at 1 minute of active recovery (1.7 MPH/0% grade)

^b CI was defined as the ratio of observed HR reserve to predicted HR reserve for a large cohort of healthy subjects previously defined in our laboratory

^c Abnormal exercise ECG was defined as any test with ≥ 1.0 mm ST deviation irrespective of whether the resting ST segments were normal, so this included non-diagnostic studies.

FAC based on age-sex adjusted performance time was greater for non-diabetics versus diabetics; it was near 100% for the non-diabetic group. Reason for termination was symptom-limited in 96% of tests; 2% of tests were terminated at patient request and another 2% according to judgment of the test monitor. The rating of perceived exertion at peak exercise averaged ~ 18 on the 6-20 Borg Scale in both groups.

Diabetics had higher resting HR and lower peak HR, HR reserve, CI and HR recovery compared to non-diabetics. Diabetic patients also had higher resting and peak exercise systolic blood pressure. Both positive exercise ECG and abnormal exercise ECG were more common in patients with diabetes. The prevalence of both abnormal HR recovery (≤ 13 beats/minute) and abnormal CI (< 0.8) was significantly higher in diabetics versus non-diabetics. A low CI using the established cut-point of < 0.8 is present in only 16% of the non-diabetics versus 39% of the diabetic patients. Using the traditional cut-point of < 13 beats/minute, abnormal HR recovery is present in only 22% of non-diabetics versus 39% of diabetics. The prevalence and significance of CI is likely altered by differential use of HR-lowering drugs in diabetics versus non-diabetics, but HR recovery, being affected principally by parasympathetic tone, should not be subject to effect of these drugs. Among the non-diabetic patients, 14,048 (70%) had no exercise HR abnormality (abnormal HR recovery or low CI), 4,724 (23%) had one abnormality and 1,424 (7%) had two abnormalities, while among diabetic patients, 539 (45%) had no abnormality, 381 (32%) had one abnormality and 280 (23%) had two abnormalities.

Effect of Diabetes on Heart Rate Variables

Table 7. shows the effect of diabetes on exercise HR variables controlling for differences between diabetics and non-diabetics in variables potentially affecting exercise HR by use of multivariate linear regression.

	Effect Simple		Effect Full	
	Model	P	Model	P
Resting HR (bpm)	+ 4.9	<.001	+ 2.9	<.001
Peak HR (bpm)	- 6.4	<.001	- 4.5	<.001
HR reserve (bpm)	- 11.4	<.001	- 7.4	<.001
HR recovery (bpm)	- 3.0	<.001	- 1.9	<.001
Chronotropic Index (CI)	- 0.128	<.001	- 0.08	<.001

Abbreviations: HR = Heart Rate

In the simple model age, sex and HR-lowering drugs were added to diabetes, while in the full model we extended it with current smoking, hypertension, abnormal exercise ECG, oral hypoglycemic drugs and insulin. Diabetes showed significant HR modifying effects in both models. In the simple model, all factors showed significant effects on each HR variable, except for female sex on HR recovery. In the full model age, female sex, HR-lowering drug, smoking, hypertension and insulin had significant HR - lowering effects on all HR variables, while oral hypoglycemic drugs did not have a significant effect on resting HR, peak HR and on HR recovery; and abnormal exercise ECG did not have a significant effect on peak HR or HR recovery.

Mortality by Diabetes and Impaired Exercise HR

Overall mortality was low. There were 1362 deaths (6.4%) over a mean follow-up of 11.9 ± 4.9 years. Differences in survival in diabetics and non-diabetics according to these two exercise HR variables are shown in **Figure 7**.

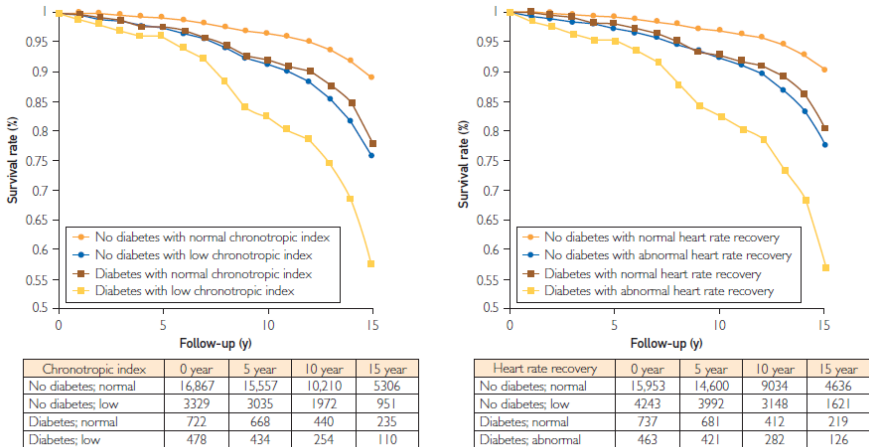


Figure 7. Survival for the first 15 years of follow-up according to presence or absence of diabetes and normal or low chronotropic index (CI) [A] and normal or abnormal heart rate (HR) recovery [B].

The reduction in survival for abnormal CI (**Figure 7A**) is very similar to the reduction seen with abnormal HR recovery (**Figure 7B**) for both diabetic and non-diabetic patients. In multivariate analysis using the simple model, which included age, sex, and use of HR-lowering drug, both $CI < 0.8$ and abnormal HR recovery contributed independently to the risk of death significantly and similarly in both diabetic and non-diabetic patients. The hazard ratio for $CI < 0.8$ was 2.21 with 95% confidence interval: 1.62 – 3.00, $P < .001$ in diabetics and 1.94 with 95% confidence interval: 1.71 – 2.20, $P < .001$ in non-diabetics. Abnormal HR recovery similarly predicted mortality (hazard ratio 2.21 with 95% confidence interval: 1.60 – 5.05, $P < .001$ in diabetics versus 1.75 with 95% confidence interval: 1.55 - 1.97,

P<.001 in non-diabetics). Only minor changes in the hazard ratios occurred with the extended model.

In **Figure 8** we further explore the relationship of mortality with the two most commonly utilized variables of exercise HR – abnormal CI and abnormal HR recovery– in diabetics versus non-diabetics.

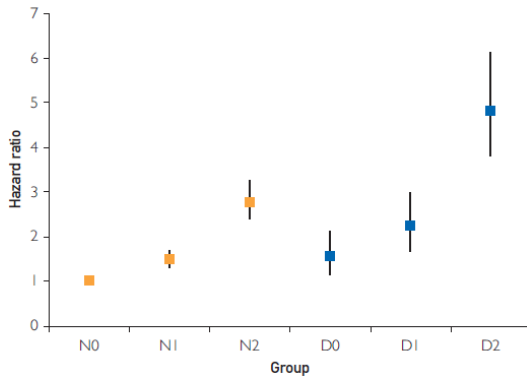


Figure 8. Hazard ratios with 95% confidence intervals for mortality by diabetes and number of exercise heart rate (HR) abnormalities (chronotropic index (CI) and HR recovery). Patients with no diabetes and 0 exercise HR abnormalities form the referent group.

Mortality increases with the number of exercise HR abnormalities in both diabetic and non-diabetic patients. To highlight the importance of exercise HR as a predictor of mortality, we compared diabetics with normal exercise HR to non-diabetics with one or two exercise HR abnormalities. Using non-diabetics with no HR abnormalities as the referent, the mortality of diabetics with no HR abnormalities (Hazard Ratio = 1.56 [95% confidence interval: 1.14 - 2.12]) is essentially the same as non-diabetic patients with one HR abnormality (Hazard Ratio = 1.50 [95% confidence interval: 1.31 - 1.71]), and the 95% confidence intervals are fully overlapped. Looking further at the importance of exercise HR in prognosis, the mortality of non-diabetic patients with both HR abnormalities is significantly higher (Hazard Ratio = 2.78 [95% confidence interval: 2.38 - 3.24]) compared to diabetics with no HR abnormalities with no overlap in the 95% confidence intervals. All models were controlled for age, sex, and use of HR-lowering drugs.

CONCLUSIONS

This study confirmed the hypothesis that HR recovery has prognostic significance in a primary prevention cohort. A unique finding is that an abnormal HR recovery predicts not only total mortality, as previously demonstrated, but it is an even stronger predictor of CV death and surprisingly predicts also non-CV death. We demonstrate that impaired HR recovery is associated with a number of well-established CV risk factors including diabetes, hypertension, current smoking and poor CRF, but it is not affected by the patient's sex or taking a HR-lowering drug. We further show that HR recovery performs equally well in all adult age groups and in both men and women and patients stratified by obesity, hypertension, or diabetes. On the other hand, HR recovery is less useful in patients with normal CRF, in current smokers, or in those taking a beta-blocker. We strongly endorse previous recommendations that HR recovery should be measured and reported on every exercise test. Impaired HR response to exercise are frequently seen in patients with diabetes, and this is predictive of excess long-term mortality beyond that seen in diabetics with a normal HR response. The stress test in diabetic patients yields much more information than just the presence of ischemia by ECG and should be interpreted more broadly to include both FAC and exercise HR for risk stratification and, potentially, to guide lifestyle interventions.

Publications directly related to the PhD dissertation

1. Sydó N*, Sydó T*, Carta KG, Hussain N, Farooq S, Murphy JG, Merkely B, Lopez-Jimenez F, Allison TG. (2018) Prognostic performance of heart rate recovery on an exercise test in a primary prevention population. *J Am Hear Assoc.* DOI: 10.1161/JAHA.117.008143
IF: 4.660 * *Equal authorship*
2. Sydó N, Sydó T, Merkely B, Carta KG, Murphy JG, Lopez-Jimenez F, Allison TG. (2016) Impaired heart rate response to exercise in diabetes and its long-term significance. *Mayo Clin Proc*, S0025-6196(15)00892-7.
IF: 6.686

Publications not related to the PhD dissertation

1. Sydó N, Kiss O, Vargha P, Édes E, Merkely G, **Sydó T**, Merkely B. (2015) Prevalence of physiological and pathological electrocardiographic findings in Hungarian athletes. *Acta Physiol Hung*, 102(2):228-37.
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2. Sydó N, Kiss O, Vargha P, Vágó H, Czibalmos Cs, Édes E, Zima E, Apponyi Gy, Merkely G, **Sydó T**, Becker D, Allison TG, Merkely B. (2016) Detailed heart rate variability analysis in athletes. *Clin Auton Res*, 26(4):245-252.
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3. Sydó N, **Sydó T**, Gonzalez Carta K, Hussain N, Farooq S, Murphy JG, Becker D, Merkely B, Lopez-Jimenez F, Allison TG. (2018) Effect of cardiorespiratory fitness on comorbidities and mortality in never, past and current smokers. Submitted to *Am J Cardiol*.
IF: 2.843