Wernhart S[1,4], Guazzi M[2], Halle M[1,3]

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Correlation of Heart Rate Recovery, Aerobic Physical Activity and Performance. A Sub-Analysis of the EURO-Ex Trial

Zusammenhang zwischen Herzfrequenzerholung und aerobem Trainingsumfang. Eine Sub-Analyse der Euro-Ex Studie

Summary

- **Objective:** Existing literature has shown heart rate recovery one minute (HRR1) after exercise termination in cardiopulmonary exercise testing (CPET) to correlate with performance, although no data exist on HRR3 and 5 in a population without manifest cardiovascular disease. We aimed to analyze whether HRR3 and 5 correlate with relative oxygen uptake at peak performance ($\dot{V}O_2$peak) and maximal power (P_{max}) as well as with weekly physical activity (PA).
- **Methods:** We conducted a sub-analysis of the Euro(pean)Ex(ercise) trial enrolling subjects between 50 and 70 years of age without manifest cardiovascular disease (n=59). Subjects underwent CPET following an individualized ramp protocol with an exercise duration between 10 and 14 minutes.
- **Results:** $\dot{V}O_2$peak (35.6±9.0 ml/kg/min) and P_{max} (245.3±80.4 W) correlated significantly with HRR1 (22.6±7.9/min, both p<.001; r=0.50 and 0.48), 3 (44.5±7.7/min, p=0.018 and 0.010; r=0.33 and 0.35) and 5 (64.8±14.0/min, p=0.002 and 0.001; r=0.77 and 0.72) in our study population (56.6±8.2 years). HRR5 correlated more strongly with PA than HRR1 and HRR3 (HRR5: p<0.001; r=0.51; HRR1: p=0.277; r=0.15; HRR3: p=0.156; r=0.20). Subjects with PA>5h/week (8.8±2.0) differed significantly from those with no regular sports in terms of HRR5 (p<0.010) and $\dot{V}O_2$peak (p<0.001).
- **Conclusions:** HRR5 is a better predictor for maximal exercise capacity than HRR1 or 3.
- **Clinical Relevance:** HRR5 should be included in exercise testing.

Zusammenfassung

- **Hintergrund:** In der Literatur konnte gezeigt werden, dass die Erholung der Herzfrequenz 1 Minute (HRR1, heart rate recovery 1 minute) nach Abbruch einer maximalen Belastung in der Spiroergometrie mit der maximalen Leistung (maximale, relative Sauerstoffaufnahme, $\dot{V}O_2$peak, bzw. Maximalleistung, P_{max}) korreliert. Es gibt keine Daten zur Bedeutung von HRR3 und HRR5 bei Patienten ohne stattgehabtes kardiovaskuläres Ereignis. Wir analysierten, ob HRR3 und HRR5 mit der $\dot{V}O_2$peak und P_{max} sowie dem wöchentlichen Trainingsumfang (PA, physical activity) korreliert.
- **Methoden:** Wir führten eine Analyse der prospektiven Multi-Center Euro(pean)Ex(ercise) Studie in unserer Abteilung nach einer Nachbeobachtungszeit von 2 Jahren durch. Hier wurden Teilnehmer zwischen 50 und 70 Jahren ohne manifeste koronare Herzerkrankung (n=59), welche eine Spiroergometrie nach einem individualisierten Rampenprotokoll durchführten, eingeschlossen.
- **Ergebnisse:** $\dot{V}O_2$peak (35.6±9.0 ml/kg/min) und P_{max} (245.3±80.4 W) korrelieren signifikant mit HRR1 (22.56±7.86/min, beide p<.001; r=0.50 und 0.48), 3 (44.45±7.65/min, p=0.018 und 0.010; r=0.33 und 0.35) und 5 (64.76±13.96/min, p=0.002 und 0.001; r=0.77 und 0.72) bei unseren Probanden (56.6±8.2 Jahre). HRR5 korreliert stärker mit PA als HRR1 und HRR3 (HRR5: p<0.001; r=0.51; HRR1: p=0.277; r=0.15; HRR3: p=0.156; r=0.20). Probanden mit PA>5h/week (8.8±2.0) unterscheiden sich signifikant von jenen ohne regelmäßige sportliche Aktivität in Bezug auf HRR5 (p<0.010= und $\dot{V}O_2$peak (p<0.001).
- **Zusammenfassung:** HRR5 ist ein besserer Prediktor für die maximale Leistungsfähigkeit als HRR1 oder 3.
- **Klinische Relevanz:** HRR5 sollte in die sportmedizinische Untersuchung als Marker integriert werden.

KEY WORDS:
Cardiopulmonary Exercise Testing, Heart Rate Recovery, Aerobic Physical Activity

SCHLÜSSELWÖRTER:
Leistungsdiagnostik, Herzfrequenzerholung, aerobe Aktivität

1. TECHNICAL UNIVERSITY OF MUNICH, *Department of Prevention, Rehabilitation and Sports Medicine, School of Medicine, Munich, Germany*
2. UNIVERSITY OF MILANO, *I.R.C.C.S. Policlinico San Donato, Heart Failure Unit Chair Exercise and Translational Science Nucleus of the European Society of Cardiology, San Donato Milanese, Milano, Italy*
3. DEUTSCHES ZENTRUM FÜR HERZ-KREISLAUF-FORSCHUNG E. V. (DZHK), *Partner Site Munich Heart Alliance, Munich, Germany*
4. GENERAL HOSPITAL KLOSTER GRAFSCHAFT-SCHMALLENBERG, *Schmallenberg, Germany*

CORRESPONDING ADDRESS:
Simon Wernhart; MD, PhD
Technische Universität München/Klinikum rechts der Isar
Präventive und Rehabilitative Sportmedizin
Georg-Brauchle-Ring 56, 80992 München
: s.wernhart@fkkg.de;
martin.halle@mri.tum.de

Introduction

Several studies indicate that regular physical activity (PA) and the level of cardio-pulmonary capacity may predict cardiovascular risk (5, 6, 13, 32, 33). Cardiopulmonary exercise testing (CPET) enables to directly measure peak oxygen uptake ($\dot{V}O_2$peak) as a marker of cardiorespiratory fitness, which allows prognostic conclusions in heart failure and chronically-ill patients (7, 18, 20, 25, 26, 27, 30, 32, 37).

Furthermore, large cohort studies have shown a negative association between $\dot{V}O_2$peak and the incidence of coronary artery disease and cardiovascular mortality in a low risk population (27, 38, 26).

The easily-measurable parameter of heart rate recovery one minute after exercise termination (HRR1) has been shown to correlate with performance and may even predict cardiometabolic morbidity ›

Table 1

Baseline Anthropometric and CPET Data. PA: Physical Activity, BMI: Body Mass Index [kg/m2], VO_2peak: Relative Oxygen Uptake at Peak Performance [ml/kg/min], P_{max}: Maximal Power[W], OUES: Oxygen Uptake Efficiency Slope, Mean Values are depicted, Standard Deviations in Parentheses, alpha<0.05.

PARAMETER	MEANS (SD)
Age	56.6 (5.2) years
no PA	0h (0)
PA<5h	2.8h (1.0)
PA>5h	8.8h (2.0)
BMI	24.3kg/m^2 (2.8)
VO_2peak	35.6ml/kg/min (9.0)
P_{max}	245.3W (80.4)
VE/VCO_2 slope	29.0 (5.9)
O_2 pulse	16.1ml/beat (5.0)
OUES	2.7 (0.9)

and mortality in a variety of populations (1, 10, 11, 19, 21, 41). HRR, which seems to have a genetic predisposition (40), also seems to be associated with microvascular angina (22), angiographical SYNTAX score classification (42) and arterial stiffness (44) as well as ventilatory constraints during exercise (12). HRR1 was shown to improve through training after myocardial infarction (14).

To our knowledge there is only one study investigating HRR after a longer period of time (HRR3 and HRR5) in patients who had suffered from transient ischemic attacks (28), but no data exists on HRR3 and HRR5 in a population without previous cardiovascular events. We want to fill this gap by analyzing the relationship between HRR1, 3 and 5 and $\dot{V}O_2$peak as well as PA in a single-centre analysis of the EuroEx population (for additional information on the trial see 24).

Methods

Prior to initiating the test, written informed consent was obtained from each participant. The design of the study was submitted to the local ethics committee and approval for the study was obtained (project number 354/14).

Subjects

We conducted a preliminary single-center sub analysis of the Euro(pean)Ex(ercise) trial (for further trial specifications see 17), enrolling subjects between 50 and 70 years of age (mean age 56.6±5.2 years) without manifest cardiovascular disease (n=59; 36 males). Assessment was performed on a routine basis in the outpatient clinic of Prevention and Sports Medicine at the Technical University of Munich. The presence of cardiovascular risk factors (assessed by questionnaires) such as hypertension (defined as a systolic pressure at rest above 140 mmHg), diabetes (HbA1c>6.5%) or hypercholesterolemia (defined as LDL cholesterol >200mg/dl) were not contraindications for study inclusion. The weekly amount of PA reported by a questionnaire was categorized into none/no regular activity, moderate (<5h/week) and high (>5h/week). All participants stated that they only performed aerobic-cyclic training (walking, running, cycling) and no high-intensity activity, defined as >14 points on a BORG scale.

Study Design

Subjects who had reported for a regular physical examination to our outpatient clinic one month earlier and had undergone incremental lactate testing (starting at 50W, with a 25W increase every three minutes; lactate taken every three minutes) to assess their fitness level underwent CPET following an individualized ramp protocol with an exercise duration ranging from eight to twelve minutes. In both the incremental lactate test as well as the ramp protocol, a standard bicycle was used. The per-minute increment in the ramp test was calculated by dividing the maximal power [W] from the lactate test by 10 (e.g. maximal power of 250W yielded a ramp increment of 25W/min).

Cardiopulmonary Testing

Prior to exercise testing, a clinical exam and a 12-lead electrocardiogram (EGG) were conducted, which had to be normal to start the test. During the test, a 12-lead ECG was continuously documented, and blood pressure was measured every minute with a standard arm cuff. Prior to the test, participants were briefed about the importance of maximal effort (a BORG scale of at least sixteen points was claimed at exercise termination) and were instructed to immediately report thoracic pain, limiting dyspnea and dizziness throughout the exam. Criteria for exercise termination were muscular exertion, significant ECG alterations (new left bundle branch block, significant ST-segment alterations, increasing number of premature ventricular beats and ventricular tachycardia), thoracic pain, dizziness, a systolic blood pressure above 250 mmHg or a systolic blood pressure drop >20 mmHg. A systolic resting blood pressure of >160 mmHg was also a contraindication for participation. At the point of exertion, the ramp was immediately stopped and participants remained on the bicycle in an upright resting position for at least five minutes.

Standard respiratory data was acquired with continuous breath-to-breath gas measurements. Daily calibration of the flow meters and gas analyzers was conducted with a syringe of known volume and predefined gas mixtures. Prior to each test, gas analyzers were checked by autocalibration. Medical residents trained in CPET interpretation defined ventilatory thresholds according to current guidelines (16), and respiratory ratios were calculated with a Cortex software (MetaSoftStudio). Heart rate recovery after one, three and five minutes was documented after exercise termination (HRR1, HRR3, HRR5). Heart rate recovery was calculated as the difference between

Table 2

Correlations (r) between Heart Rate Recovery (HRR: 1, 3 and 5 Minutes after Exercise Termination) and Relative Oxygen Uptake at Peak Performance (relVO_2peak) as well as Maximal Power (P_{max}) and Physical Activity (PA), alpha<0.05.

PARAMETER	HRR1	HRR3	HRR5
VO_2peak [ml/kg/ml]	p<0.001; r=0.50	p=0.18; r=0.33	p=0.002; r=0.43
P_{max} [W]	p<0.001; r=0.48	p=0.010; r=0.35	p=0.001; r=0.46
PA [hours/week]	p=0.277; r=0.15	p=0.156; r=0.20	p=<0.001; r=0.51

the heart rate at exercise termination minus the heart rate after one (HRR1), three (HRR3) and five (HRR5) minutes during passive recovery on the ergometer in a sitting and resting position.

A telephone follow-up was conducted every six months for a period of 24 months, inquiring about cardiovascular events and the participants' weekly training hours.

Statistics

Statistical analysis was performed with a standard software package (SPSS 23). Normality was assessed and demonstrated with the Kolmogorow-Smirnow test and Bonferroni corrections for multiple testing were conducted. ANOVA was used to analyze differences between the three groups of PA. Quantitative measures were described by means and standard deviations, while associations between quantitative measures were calculated using Pearson's correlation coefficient. In order to adjust for possible confounders such as age, sex, diabetes, hypertension, dyslipidemia and body mass index (BMI), linear regression models were fit to the data and partial correlation coefficients were estimated. A level of significance of α=0.05 was used.

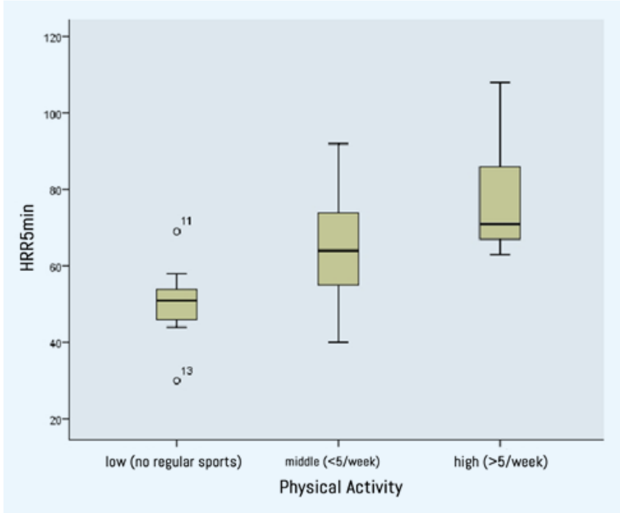

Figure 1

Relationship between heart rate recovery 5 minutes after exercise termination (HRR5; in beats per minute) and aerobic physical activity (training hours per week). Standard deviations are depicted in vertical bars.

Results

The general cardiovascular risk profile was moderate in our population with only five (8.5%) smokers, eleven (18.6%) diabetics (five, 8.5%, with dietary control and six, 10.2%, medically-controlled, none were insulin-dependent) eleven (18.6%) hypertensives (all medically-controlled) and seventeen (28.6%) subjects with dyslipidemia (ten without medical treatment, six set on statins and one on fibrates). None of our participants took beta-blockers.

Nine participants reported none or no regular activity, 37 moderate (<5h/week; mean activity: 2.8±1.0 hours/week) and 13 high (>5h/week; n=13; mean activity: 8.8±2.0 hours/week) PA.

Mean BMI was 24.3±2.8 kg/m2, mean relative $\dot{V}O_2$peak was 35.6±9.0ml/min/kg and peak power 245.3±80.4 W, respectively. VE/VCO_2 slope (mean 29.0±5.9) and O_2peak pulse (16.1±5.0 ml/heartbeat) were within normal limits according to current ESC guidelines (14). Flattening of O_2 pulse during exercise was observed in nine individuals; however, none of our participants displayed exercise oscillatory ventilation patterns (EOV). Mean oxygen uptake efficiency slope (OUES; 2.7±0.9, see Table 1) and $\Delta\dot{V}O_2/\Delta W$ (8.9ml/min/W) as well as resting (32.8±4.0 mmHg), minimal (27.8±5.0 mmHg) and peak (36.2±5.4 mmHg) $PETCO_2$ were within normal limits according to ESC guidelines (12). Means of peak heart rate (162.1±14.2 min) as well as peak systolic (206.4±27.3 mmHg) and diastolic (86±11 mmHg) blood pressure did not suggest cardiovascular limitations during exercise testing (see Table 1).

Relative $\dot{V}O_2$peak and P_{max} were strongly correlated with heart rate recovery after one (22.6/min±7.9; both p<.001; r= 0.50 and 0.48), three (44.5/min±7.7, p=0.018 and 0.010; r=0.33 and 0.35) and five (64.8/min±14.0, p=0.002 and 0.001; r= 0.43 and 0.46, see Table 2) minutes, as well as with peak O_2 pulse (both p<.001; r=0.77 and 0.72) after correcting for confounders (age, sex, dyslipidemia, hypertension, diabetes, smoking, sex and BMI). VE/VCO_2 did not significantly correlate with exercise performance (p=0.49 and 0.90; r=0.01 and 0.02). Furthermore, heart rate recovery after five minutes was significantly correlated with the weekly amount of PA (p<.001; r=0.51; see figure 1), but not after one (p=0.277; r=0.15) and three (p=0.156; r=0.20) minutes following exercise termination. Therefore, only HRR5 correlated with PA, while HRR1 and HRR3 did not. The group of PA>5h significantly differed from the group with no regular sports activity in terms of HRR5 (p<.010), while PA>5h and PA<5h (p=0.53) as well as PA<5h and no sports (p=0.21) did not show significant differences.

In a linear regression model, the weekly amount of PA (p<.001; beta=0.481) and age (p=0.025; beta=-0.268) – but not BMI (p=0.772; beta=-0.03) – had a significant impact on relative $\dot{V}O_2$peak (R2=0.422), while BMI (p=0.008; beta=0.263), the weekly amount of PA (p=<.001; beta=0.475) and age (p=0.012; beta=-0.277) significantly influenced P_{max} (R2=0.51).

Relative $\dot{V}O_2$peak only significantly differed between the group with no regular sports and PA>5h (<0.001), while there was no difference between PA<5h and >5h (p=0.34) as well as between PA<5h and no sports (p=0.24).

The test only had to be stopped with one patient due to an exaggerated blood pressure response (260mmHg at 100W). Fifty out of 59 patients reported muscular fatigue as a reason for exercise termination, while nine stated that dyspnea was responsible for stopping the test. Thoracic pain was not reported and significant ECG alterations did not occur. In two patients, intermediate, asymptomatic right bundle branch block occurred, while three other patients displayed several asymptomatic premature ventricular complexes.

According to the telephone follow-up, no cardiovascular endpoint was suffered during the first two years. Hours of PA remained the same in seventeen, decreased in one, and increased in eight participants.

Discussion

Our EuroEx sub-analysis showed a significant correlation between heart rate recovery after exercise termination (HRR1, 3 and 5) and performance (P_{max} and relative $\dot{V}O_2$peak, hypothesis 1 accepted). HRR1 and HRR5 achieved higher correlation coefficients than HRR3. This is interesting because studies have generally used HRR1 as a measure of recovery, although according to our data HRR5 may be as valuable. In the literature HRR5 was only used by Li et al. 2019 (28) in patients who had suffered from transient ischemic attacks (TIA) and was negatively associated with quality of life. Our similarly aged EuroEx population performed better than their TIA group (64.8±14.0/min vs. 54±16.0/min).

Only HRR5 was significantly associated with the weekly amount of PA (H2 can be accepted), which was the strongest predictor of exercise performance (in terms of relative $\dot{V}O_2$peak and P_{max}). We did not find a correlation between HRR1 and HRR3 with PA, but only for HRR5 and PA. We categorized PA into three categories, defining the most active group with >5h/week (300 min/week), which is double the recommendations of the 2016 ESC prevention guidelines (36). In our study, those individuals who participated in sports >5 hours/week were clearly superior in HRR5 and overall performance ($\dot{V}O_2$peak and P_{max}). On the whole, HRR5 may even be a better parameter than the established HRR1 to assess performance capacity.

In our study, PA was merely defined through exercise duration, whereas exercise intensity – usually defined through METs (metabolic equivalents) – was not assessed. However, given most of our participants performed aerobic, cyclic activities, we do not anticipate a relevant variation in PA intensity in our population, which could have altered our results (for literature on high intensity and moderate training see 2, 15, 27, 29, 31, 32, 34, 35, 39, 43).

In the last decade large cohort studies have shown a clear association between cardiorespiratory fitness ($\dot{V}O_2$peak) and cardiovascular morbidity and mortality (26, 27, 38). Recently Letnes et al. (27) published data on a healthy population without antihypertensive medication from the HUNT-3 cohort, who were younger (48.2±13.5 years vs. 56.6±5.2 years) than our population and performed better in terms of $\dot{V}O_2$peak (in males 44.4±9.2ml/kg/min vs. 35.6±9.0 ml/kg/min) and O_2 pulse (20.9±3.9ml/heartbeat vs. 16.1±5.0ml/heartbeat). A large Finnish study in a population without manifest cardiovascular disease and a low risk profile also showed higher mortality rates with lower $\dot{V}O_2$peak (26). The Baltimore Longitudinal Study of Aging (38) showed a reduced risk of coronary events (CE) in a healthy population <65 years of age with increasing $\dot{V}O_2$peak (hazard ratio 0.53). Compared to these large trials the EuroEx study population is quite unique, because patients with manifest cardiovascular risk factors, yet no previous events, were included.

In our study $\dot{V}O_2$peak was indexed by total body weight. However, quite recently, data from the SHIP-2 and SHIP-TREND study have demonstrated that body cell mass and fat free mass measured through bioelectrical impedance analysis may be more appropriate markers to compare fitness in subjects with different body shapes (23). This may especially be important in the analysis of obese patients, although this does not reflect our population (BMI 24.3±2.8kg/m²).

Although some benefits on the predictive value of CPET parameters on morbidity (such as VE/VCO_2 slope, EOV, OUES and O_2 pulse) have been documented in the literature (3, 4, 8, 9, 25), we did not observe any cardiovascular events in our short-term follow-up and therefore cannot draw any conclusions.

Our study is the first to observe that HRR5 is a better parameter than HRR1 in terms of drawing conclusions about performance capacity and PA. Whether HRR5 can also function as a predictor of mortality – similar to HRR1 – remains unclear.

Conflict of Interest
The authors have no conflict of interest.

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