Original articles

One-minute heart rate recovery after cycloergometer exercise testing as a predictor of mortality in a large cohort of exercise test candidates: substantial differences with the treadmill-derived parameter

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Key words:
Electrocardiography; Exercise test; Heart rate; Mortality; Prognosis.

Background. **Previous work showed a strong inverse association between 1-min heart rate recovery (HRR) after exercising on a treadmill and all-cause mortality. The aim of this study was to determine whether the results could be replicated in a wide population of real-world exercise ECG candidates in our center, using a standard bicycle exercise test.**

Methods. **Between 1991 and 1997, 1420 consecutive patients underwent ECG exercise testing performed according to our standard cycloergometer protocol. Three pre-specified cut-point values of 1-min HRR, derived from previous studies in the medical literature, were tested to see whether they could identify a higher-risk group for all-cause mortality; furthermore, we tested the possible association between 1-min HRR as a continuous variable and mortality using logistic regression.**

Results. **Both methods showed a lack of a statistically significant association between 1-min HRR and all-cause mortality. A weak trend toward an inverse association, although not statistically significant, could not be excluded.**

Conclusions. **We could not validate the clear-cut results from some previous studies performed using the treadmill exercise test. The results in our study may only "not exclude" a mild inverse association between 1-min HRR measured after cycloergometer exercise testing and all-cause mortality. The 1-min HRR measured after cycloergometer exercise testing was not clinically useful as a prognostic marker.**

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Introduction

The fall in heart rate immediately after exercise is considered to be a function of the reactivation of the parasympathetic nervous system[1,2]. A landmark paper published 3 years ago drew the deserved attention to the prognostic implications of changes in heart rate immediately after exercise[3]. The authors showed that a low rate of recovery of the heart rate, measured 1 min after exercising on a treadmill – specifically, a 1-min heart rate recovery (HRR) ≤ 12 beats – was an independent prognostic marker in their study population; it was an all-cause mortality marker at least as powerful as simple. They specifically focused on the overall mortality as an unbiased, hard endpoint[4,5].

Since then many investigators tested the same hypothesis, using slightly different exercise protocols and assessing populations which were very heterogeneous in their baseline characteristics; not surprisingly, these studies yielded controversial results[3,6-10].

Although they generally confirmed the ability of low HRR values (measured after treadmill exercise testing) to function as a prognostic factor for all-cause mortality, the cut-points and time from exercise used to measure this parameter varied greatly across these studies.

No studies addressing the possible prognostic value of 1-min HRR when it is measured after exercise on a cycloergometer have been published in the literature to date.

The different characteristics in the type of exercise before measuring HRR (for example weight-bearing vs non-weight-bear-

ing) may not only change the best absolute number to choose as a prognostically significant cut-point, but they could also change the prognostic power of the parameter itself.

The aim of this study was to determine whether previous results could be replicated in a population of "real world" exercise ECG candidates who underwent standard bicycle exercise testing.

Methods

Patient population. The study cohort consisted of 1420 consecutive patients (mean age 55 ± 10 years, range 25-85 years) undergoing evaluation of chest pain for suspected/known coronary artery disease. The patients were referred to our exercise ECG service for a first symptom-limited exercise test between January 1991 and December 1997. In accordance with the recently published American College of Cardiology/ American Heart Association guidelines on exercise testing exclusion criteria[11], patients were excluded if they were not in sinus rhythm at the beginning or during the test, had a previous revascularization procedure, had an implanted pacemaker, congestive heart failure, use of digoxin, congenital or valvular heart disease and a preexcitation syndrome or left bundle branch block. Patients were also excluded if they lived in a village/ town not included in the 15 biggest villages/towns around our hospital (because of technical problems with demographic data) or if the exercise protocol used was different from the one selected for the study and described in the text. All patients gave their informed consent before testing.

Clinical data. Before the patients were tested, a brief interview was conducted to collect data on symptoms, medications and previous cardiac events.

Patients were classified as having been referred to exercise testing because of 1) chest pain with no history of coronary disease or 2) chest pain with previous myocardial infarction (MI), as assessed on the basis of their history and/or ECG abnormalities indicating old/established MI.

The use of medications was classified as beta-blocker use or not during the last 3 days before the test. In patients with previous MI, the decision to withdraw beta-blockers was left to the referring physician; otherwise they had to be withdrawn at least 3 days before testing.

Exercise testing. Exercise testing of all the patients included was conducted according to the protocol routinely used in our center: the 70 rpm and 25 W × 2 min protocol; the recovery phase started with 5 W/s workload reductions to a goal of 30 W for the first minute, then 20 W. The patient was encouraged to maintain 60 to 70 rpm during the recovery phase.

Midway through each stage of exercise, at peak exercise, and 1 min after the cessation of exercise, data on symptoms, heart rate and rhythm and blood pressure (as measured by indirect arm-cuff sphygmomanometry) were collected. The patients were encouraged to reach symptom-limited maximal exercise; the achievement of the target heart rate (based on age) alone was not a sufficient reason for the termination of testing.

The value for HRR was defined as the reduction in the heart rate from the rate at peak exercise to the rate 1 min after the beginning of the recovery phase.

Follow-up. The mean follow-up was 8 years (range 5-11 years). The primary endpoint was all-cause mortality.

Statistical analysis. All-cause mortality was used as the outcome for follow-up. The mean ± SD was used to describe continuous data. Differences between groups were compared using the Student's t-test for unpaired data or the χ^2 test, as appropriate. Survival analysis was performed using Kaplan-Meier curves. Logistic regression was used to examine the influence of prognostic factors. Hazard ratios were calculated along with their 95% confidence intervals.

In the logistic regression analysis, 1-min HRR was kept continuous, avoiding arbitrary cut-points. The relationship of 1-min HRR with outcome is assumed to be log-linear, i.e. the risk (expressed as the log odds ratio or log hazard ratio) either increases or decreases linearly as the variable increases. In previous studies many researchers preferred to categorize patients into high- and low-risk groups on the basis of their threshold or cut-point[3,5-10]. In order to compare our results to those of other articles, in this study both the above-described approaches were used. If a cut-point is used, ideally it should not be determined using a data-dependent process. For this reason, we felt that it would be reasonable to test the following pre-specified cut-points:

- the median value in our population,
- the best discriminating value in the landmark study where treadmill was used as the exercising mean (12 beats)[3],
- the pre-specified 25th percentile from the present study (just as 12 beats corresponded to the 25th percentile in the aforementioned study[3]).

For all the statistical analysis we used the StatsDirect® (Cheshire, UK) software package version 1.9.8.

Results

Baseline patient characteristics. One thousand four hundred and twenty patients met all the inclusion criteria. The baseline characteristics and pre-test prognostic value of a history of MI are shown in table I; 97 patients

died during follow-up (6.83%). Fifteen percent of the patients had previous MI, while 85% were referred to "rule-out" a cardiac origin of chest pain in subjects with no previous history of coronary artery disease. HRR characteristics of patients after testing are reported in table II.

Ninety-eight patients (6.9%) were lost to follow-up.

The distribution of age, 1-min HRR and deaths across subgroups are reported in table III.

Heart rate recovery and mortality. All of the three pre-specified tested cut-points did not show any statistically significant result (Table IV). Figure 1 shows the Kaplan-Meier survival curves for 1-min HRR ≤ 22 and > 22.

When logistic regression was used to test the pre-specified cut-points, it confirmed the lack of association between 1-min HRR and all-cause mortality. When keeping 1-min HRR continuous, logistic regression showed no statistically significant association between the fall in heart rate and all-cause mortality (Table V).

When, on the basis of the presence or absence of a previous MI, the study population was divided into two groups, only the group with previous MI showed a borderline statistical significance for a mild inverse association between 1-min HRR and mortality (Table VI).

Table I. Baseline patient characteristics.

No. patients	1420
Age (years)	55 ± 10
Sex (M/F)	927/493
Previous myocardial infarction	215 (15.1%)
Use of beta-blockers in the last 3 days	116 (8.2%)

Table II. Characteristics of the patients after cycloergometer testing.

Mean 1-min HRR	23 ± 9
Median 1-min HRR	22
Lower quartile	16
Upper quartile	28
Positive test-ECG criteria	410 (28.8%)
Peak HR ≥ 85% of the maximal predicted value	1054 (74.2%)

HR = heart rate; HRR = heart rate recovery.

Table IV. Hazard ratios (HR) and 95% confidence intervals (CI) for the pre-selected cut-points.

	HR	95% CI	Median survival
HRR ≤ 12 vs > 12	1.54	0.82-2.89	84 vs 96
HRR ≤ 16 vs > 16	1.59	1.00-2.53	84 vs 96
HRR ≤ 22 vs > 22	1.39	0.93-2.01	96 vs 96

HRR = heart rate recovery.

Discussion

Previous studies and population selection. This is the first study performed using the cycloergometer with the aim of evaluating the prognostic value of HRR; of course we could compare the study design, population characteristics and many other variables with those of previous studies, but we must emphasize that results cannot be compared, as previous studies were always performed using the treadmill test as the only exercise modality.

Since measuring HRR is intended to provide another parameter in addition to those of the standard exercise test, we found that it would be most appropriate to determine its value in a study population specifically not including asymptomatic or revascularized patients; the usefulness and interpretation of the results of exercise testing is in fact at least controversial in these categories of subjects[11,12].

Nonetheless, most of previous studies selected populations in which the prevalence of cardiac ischemia symptoms was either low or not clearly stated[3,5,7-9].

The only study performed in a population with no asymptomatic and no revascularized subjects was carried out in a US Veterans Affairs center, with a 100% male population and a 42% prevalence of previous MI and consequently a very high mortality (19%)[6].

Our study population consisted of 35% females, a 15% previous MI prevalence and had a mortality slightly less than 7% (after a similar follow-up period); hence, with regard to these important baseline characteristics our population was unique and hardly comparable to those of previous studies. Another significant difference is that, unlike previous ones, our study was not performed in a tertiary care center, but in a medium-sized community hospital, at least in part avoiding referral selection bias.

Table III. Baseline characteristics and 1-min heart rate recovery (HRR) across the different subgroups.

	No BB group	No previous MI group	Both	Total
No. patients	1304	1205	1127	1420
Age	55 ± 10	55 ± 10	55 ± 10	55 ± 10
Mean 1-min HRR	23 ± 9	23 ± 9	23 ± 9	23 ± 9
Median 1-min HRR	22	22	22	22
Deaths	87 (6.67%)	70 (5.80%)	63 (5.59%)	97 (6.83%)

BB = beta-blocker; MI = myocardial infarction.

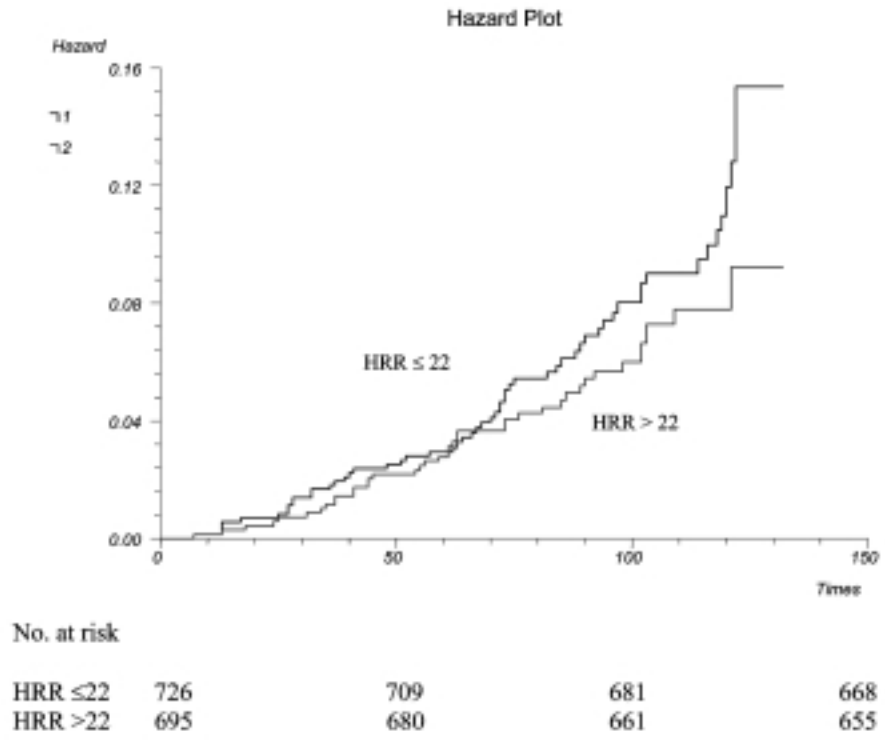

Figure 1. *Cumulative proportions of events for a heart rate recovery (HRR) of 22 (median) as cut-point. Time since test on X-axis (months); proportion of patients who died on Y-axis.*

Table V. Logistic regression - odds ratios (OR) of pre-specified cut-points and keeping the heart rate recovery (HRR) as continuous variable.

Parameter	OR	95% CI
Pre-specified cut-points		
HRR ≤ 12	1.12	0.64-1.97
HRR ≤ 16	0.98	0.52-1.84
HRR ≤ 22	0.84	0.47-1.51
Continuous variable	0.98	0.95-1.00

HRR 12 is the cut-point reported in another study[3]; HRR 16 is the lower quartile found in our study; HRR 22 is the median of the values found in our study. CI = confidence interval.

Table VI. Logistic regression adjusted according to the presence/absence of a history of previous myocardial infarction (MI).

	Parameter	OR	95% CI
Previous MI	HRR	0.94	0.90-0.99
No previous MI	HRR	0.99	0.97-1.02

CI = confidence interval; HRR = heart rate recovery; OR = odds ratio.

All of these dissimilarities could theoretically explain the very different results in our study compared with those of the six previously published studies investigating the prognostic power of HRR using the treadmill.

Previous studies and statistics. In previous studies many researchers preferred to use a threshold or cut-point for 1-min HRR to categorize patients into high- and low-risk groups[3,5-10]. This type of analysis discards potentially important quantitative information and considerably reduces the power to detect a real association with outcome[13]. Some investigators computed the statistical significance level for all possible cut-points and then selected the cut-point with the smallest p value. As they correctly state in their paper[3], there are some conceptual problems associated with this so-called "optimal" approach[14,15]. In particular, the p values and regression coefficients resulting from this analysis are biased. The assumption of a constant risk on either side of the cut-point is unrealistic, and the prognostic value of the variable of interest is overestimated. The bias is carried across into subsequent multiple regression analyses.

Keeping the variable (1-min HRR) continuous has the considerable advantages of retaining all the information and avoiding arbitrary cut-points; hence, we preferred this method and only in a second instance did we perform the cut-point-based analysis, in order to compare the results of our study with previously published data on 1-min HRR.

Interpretation of results. We could not validate the clear-cut results from previous studies performed using the treadmill exercise test, that showed some specific values of 1-min HRR as being able to distinguish two groups with a very different all-cause mortality. The re-

sults of our study did not show any statistical significance for an association between the variable and mortality.

At best, our data can only not exclude a mild inverse association between 1-min HRR measured after cycloergometer exercise testing and all-cause mortality, particularly in the subgroup of patients with previous MI. Our interpretation of the data is that 1-min HRR measured after cycloergometer exercise testing was not clinically useful as a prognostic marker in a population of subjects undergoing evaluation of chest pain for suspected coronary artery disease.

Prognosis and diagnosis. In our study 1-min HRR was tested for its prognostic power: no speculation about its clinical usefulness in increasing the diagnostic accuracy of the exercise test for coronary artery disease can be made.

In fact, in only one study was an attempt made to establish whether low values of 1-min HRR (measured after the treadmill test) were associated with a higher incidence of coronary artery disease (routinely diagnosed using the gold standard coronary angiography) and, surprisingly, it did not show any statistically significant association. Nonetheless, in the very same study, this parameter itself (i.e. 1-min HRR) was found to have a strong prognostic predictive power; hence it is hypothesized that 1-min HRR and the presence of coronary artery disease may be independent prognostic factors[6]. The independent prognostic power of an abnormal HRR with respect to the presence of coronary artery disease has been recently confirmed in an elegant study by Vivekananthan et al.[16].

While 1-min HRR measured after cycloergometer testing did not show any clinically relevant prognostic power, the lack of routine coronary angiography in our study population did not permit us to investigate the aforementioned potential association between 1-min HRR and the presence of coronary artery disease. Similarly, we cannot infer anything about the potential usefulness of the parameter itself raising exercise test accuracy in the gatekeeping role with respect to coronary angiography, i.e. helping to stratify intermediate-risk patients into low or high risk.

Study limitations. The clinical data regarding the patients in our study population are limited because of its retrospective nature. We had to discard many categories of clinical data about the history of our subjects (diabetic or hypertensive status for example) simply because we did not feel sure that the whole population was consistently and routinely interrogated about these conditions: so we could neither correct for these variables nor evaluate their influence on the outcome in multivariate analysis.

We had a consistent number of subjects who were lost to follow-up and this could theoretically have impaired our statistics. All the same:

• the method of data collection for establishing the alive/dead status was a simple demographic query to the authorities of the 15 biggest villages around our hospital and it tends to exclude that the lost to follow-up group had a different outcome (higher mortality) with respect to subjects with a known outcome. In fact, lost to follow-up subjects were simply missing in the residents' list of the village where they used to live many years before (at the time of inclusion) and this is easily explained by the fact that for personal/work reasons subjects may have moved to other cities during the long follow-up period;

• we compared the prevalence of lost to follow-up risk factors/parameters with the same parameter prevalence and distribution in the population with a known outcome: no statistically significant difference in 1-min HRR and other risk factors between the two groups was found, suggesting that the lost to follow-up group was homogeneous with the rest of the population (Table VII); moreover, when the subjects were divided into three subgroups on the basis of outcome (alive vs dead) and of known outcome vs lost to follow-up (Table VIII), it appeared that the lost to follow-up group overlapped with the "alive group" in terms of a predicted heart rate ≥ 85% and of the prevalence of positive tests: one more clue to reasonably exclude that the data of the lost to follow-up group would have modified our conclusions;

• when logistic regression analysis is performed omitting the lost to follow-up group ($p = 0.06$), it confirms the previous, non-statistically significant findings obtained in the whole population and reported in table V.

Table VII. Risk factor distribution for the lost to follow-up vs patients with a known outcome.

	Characteristics of all patients, excluding those lost to follow-up	Same characteristics in patients lost to follow-up	p
No. patients	1322	98	
Age (years)	55 ± 10	55 ± 11	NS
Sex (M/F)	867/455 (66%/34%)	60/38 (61%/39%)	NS
Prior myocardial infarction	190 (14.3%)	15 (15.3%)	NS
Beta-blockers in the last 3 days	114 (8.6%)	9 (9.1%)	NS
1-min HRR	23 ± 9	23 ± 10	NS

HRR = heart rate recovery.

Table VIII. Distribution of subjects reaching 85% of the predicted maximal heart rate (HR) and the prevalence of a positive test across the subgroups.

Subgroup	No. patients	≥ 85% predicted maximal HR (%)	Positive test (%)
Alive	1225	75	28
Dead	97	58	43
Lost to follow-up	98	76	27

We could not gather any follow-up information in our study population, apart from the alive/dead status. For this reason, we could not censor patients who underwent revascularization procedures and who could have influenced the outcome; nonetheless, although this influence cannot be excluded, it still has to be proved in clinical studies[6].

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