Correlation of Modification of Heart Rate Recovery with Adaptation to Myocardial Ischemia in a Model of Sequential Exercise Testings

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Background: Heart rate recovery (HRR) has been identified as a reliable predictor of cardiac mortality, correlated with autonomic tone. In a model of sequential exercise testings, we investigated the reproducibility of HRR and the association between HRR modification and myocardial adaptation to ischemia.

Methods: We studied 128 patients (mean age 62 ± 9 years, 83% males) with angiographically documented coronary artery disease (CAD) and a first positive exercise testing, who agreed to undergo a second exercise testing after 24 hours.

Results: HRR was increased from 25 ± 10 beats/min at the first exercise testing to 30 ± 13 beats/min at the second exercise testing ($P < 0.001$). Thereafter, participants were divided into two groups: Group I comprised 88 patients who presented augmentation of the HRR in the first compared to the second exercise testing, while group II comprised 40 patients who presented unchanged or reduced HRR. The rate-pressure product (RPP) at 1 mm ST-segment depression (ischemic threshold) at the second compared to the first exercise testing were significantly improved in group I patients (2345 ± 3429 mmHg/min), while it was worsened in group II patients (-630 ± 2510 mmHg/min) ($P < 0.001$).

Conclusions: In a model of sequential exercise testings, myocardial adaptation to exercise-induced ischemia was associated with favorable modification of HRR.

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Heart rate recovery (HRR) at the first minute of the postexercise period has been shown to predict increased mortality among patients with heart disease.^{1–7} Although its prognostic value has been well established, the exact mechanisms underlying these observations have not been clarified yet. The first rapid phase of HRR has been ascribed to parasympathetic reactivation. Thus, reduced HRR may deflect impaired autonomic tone, which has been convincingly associated with increased risk of arrhythmogenesis and sudden cardiac death. However, in most previous studies, HRR has been

related with all-cause and not only with cardiac mortality.

Although in terms of pathophysiology, myocardial adaptation to ischemia has been ascribed to factors such as the training-effect coronary vasodilation and opening of collateral vessels, attenuation of ischemic signs during sequential exercise testings could also represent an aspect of exercise-induced myocardial ischemic preconditioning in humans. Notably, exercise-induced myocardial preconditioning phenomena in humans have been associated with favorable metabolic effects and

rate-pressure product (RPP) changes, which represent improved myocardial oxygen consumption.^{8,9} Furthermore, in previous studies, using several models of exercise-induced myocardial ischemia, both a first and a second "window" of anti-ischemic protection have been recognized.¹⁰⁻¹³ This phenomenon features a basic characteristic of ischemic preconditioning mechanism, which provides its cardioprotective effects for a "first window" of 2 or 3 hours after a first ischemic event and subsequently reappears 24-72 hours later, as a "second window" protection. The early phase seems to provide stronger cardioprotection. However, the longer duration of the late phase, as well as its protective effect against myocardial stunning, increases its possible significance in clinical practice.

In this study, we tested HRR reproducibility in patients with exercise-induced ischemia, and investigated whether any modification of autonomic cardiac control (assessed by the HRR) could be related to favorable exercise-induced myocardial adaptation.

METHODS

Study Protocol

We studied 128 patients (mean age 62 ± 9 years, 83% males), with exercise-induced myocardial ischemia and angiographically documented coronary artery disease (CAD; detection of at least one major coronary branch with a stenosis $\geq 70\%$ in diame-

ter), who had agreed to undergo a second exercise testing 24 hours after a first positive exercise testing. Baseline characteristics and angiographic data of the studied patients are presented in Table 1. Patients with prior extended Q-wave myocardial infarction, heart failure, left ventricular hypertrophy, severe valvular or congenital heart disease, cardiomyopathy or acute myocarditis, permanent atrial fibrillation, preexcitation syndrome, left bundle branch block, permanent paced rhythm, atrioventricular block, chronic digitalis treatment, pulmonary and/or systemic infection, and chronic respiratory disease were excluded from the study.

All patients were instructed to avoid any form of excessive physical activity for the last 2 days before the protocol, in order to eliminate the confounding effects of an ischemic episode on the possible induction of ischemic preconditioning phenomena before the first exercise testing.

All cardiovascular drugs were discontinued 48 hours before the first exercise testing, as well as during the 24-hour period between the two exercise testings. The use of sublingual nitroglycerine during angina episodes was allowed during this period. However, the examination was rescheduled when such an episode occurred within 24 hours before the first exercise testing.

The study was approved by our hospital's ethics committee. Before obtaining informed consent, the study protocol was explained in detail to the study patients.

Table 1. Baseline Characteristics and Angiographic Data of the Studied Patients

	Total (N = 128)	Group I (N = 88) (HRR Increase)	Group II (N = 40) (HRR Stable or Decreased)	P Value
Baseline characteristics				
Age (years)	62 ± 9	61 ± 9	63 ± 9	0.376
Male gender (%)	83	82	85	0.658
BMI (kg/m^2)	27.3 ± 3.2	27.4 ± 3.4	27.2 ± 2.8	0.769
Smokers (%)	27	25	33	0.378
Hypercholesterolemia (%)	67	68	65	0.722
Hypertension (%)	46	48	43	0.582
Diabetes (%)	18	14	28	0.058
Angiographic results				
One-vessel disease (%)	48	50	45	0.600
Two-vessel disease (%)	34	35	33	0.763
Three-vessel disease (%)	17	15	23	0.283
Number of diseased vessels	1.69 ± 0.75	1.65 ± 0.7	1.78 ± 0.8	0.376
LAD disease (%)	67	68	65	0.722
LVEF	50 ± 3	50 ± 3	50 ± 3	0.978

HRR = heart rate recovery; BMI = body mass index; LAD = left anterior descending; LVEF = left ventricular ejection fraction.

Exercise Testing

All patients underwent two treadmill exercise testings, which were performed during a time window of 9:00 to 12:00 AM in the first and the next day, on a Marquette case system (G-Medical System, Milwaukee, WI, USA), according to the multistage Bruce protocol. The second exercise testing was performed the next day (with a minimum interval of 24 hours), by the same personnel.

Blood pressure was measured every minute during exercise and the recovery period, with sphygmomanometer. Exercise was terminated because of severe angina, fatigue, dyspnea, or severe arrhythmias. In the absence of symptoms, the test was terminated at the occurrence of a 3 mm ST-segment depression or a 1 mm ST-segment elevation, a decrease in systolic blood pressure ≥ 10 mmHg, or an inability to exercise further because of fatigue. An ischemic ST-segment response was defined as horizontal or down-sloping ST-segment depression of ≥ 1 mm below the baseline, taken 60 ms after the J point.

Electrocardiographic measurements were performed with a magnifying lens, by two of the investigators, who were unaware of the angiographic results. The intra- and interobserver variability for ST-segment changes were 0.07 ± 0.05 and 0.08 ± 0.05 mm, respectively.

Heart Rate Recovery

Heart rate recovery was defined as the difference between the peak heart rate and the heart rate at the first minute of the recovery period. We did not use a postexercise cool-down period immediately after the termination of the exercise testing.

Although a certain normal limit for HRR has not been officially adopted, a cutoff value of 12 beats/min has been originally proposed to identify patients in high risk.¹ However, when a postexercise cool-down period is not used, a cutoff value of 18 beats/min has been proposed.⁵ We used both these values in our analysis.

Coronary Arteriography and Left Ventriculography

All patients underwent left ventriculography in the 30° right anterior oblique projection, at 40 frames/sec. The area-length method was used for the calculation of the left ventricular ejection fraction. All patients underwent selective coronary ar-

teriography, using the percutaneous (Judkins) technique. The left coronary artery was visualized in the 60° left anterior oblique, in the 30° right anterior oblique, and in the left lateral, with 30° cranial angulation positions. The right coronary artery was visualized in the 60° left anterior oblique and the 30° right anterior oblique positions.

Significant coronary stenosis was considered in the presence of more than 70% diameter narrowing in the lumen of the left anterior descending, the left circumflex, and the right coronary artery, or a diameter narrowing of at least 50% in the left main coronary artery. The interpretation was performed by two investigators, who were unaware of exercise results.

Statistical Analysis

Values are expressed as mean $\pm$ one standard deviation. Pearson's chi-square test for categorical variables and Student's *t*-test for continuous variables were employed to compare baseline characteristics of the groups of interest. Logistic regression analysis was employed in order to detect possible significant associations between a dichotomous dependent variable and a number of independent ones. Variable selection was terminated when no candidate variables for entry were significant at $P < 0.05$, and all those selected for entry remained significant at $P < 0.10$. All tests were considered to be significant at a 0.05 level of statistical significance. Statistical analyses were performed with SPSS statistical software (version 11.5, SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics and angiographic results of the 128 patients are presented in Table 1. The comparison of exercise parameters between the first and second exercise testing for the 128 patients is presented in Table 2. Although an improvement is revealed in most parameters, a statistically significant change is detected only in maximal ST-segment depression ($P = 0.005$), in time to 1 mm ST-segment depression ($P < 0.001$) and in HRR ($P < 0.001$), while difference in maximal exercise duration tended also to be statistically significant ($P = 0.084$). Maximum *RPP* and *RPP* at 1 mm ST-segment depression seem to augment, although not significantly. Finally, it is remarkable that 12 patients had a negative second exercise testing.

Table 2. Comparison of Exercise Parameters between the First and Second ET

Clinical and Exercise Parameters	1st ET (N = 128)	2nd ET (N = 128)	P Value
Exercise duration (sec)	452 ± 141	482 ± 118	0.084
Maximal ST depression (mm)	2.32 ± 0.8	2.01 ± 0.9	0.005
Patients with 1 mm ST-segment depression	128	116	<0.001
Patients who presented angina	52	42	0.195
Maximum <i>RPP</i> (mmHg/min)	25,643 ± 4691	26,279 ± 4264	0.258
<i>RPP</i> at 1 mm ST depression at the 1st exercise testing (mmHg/min)	20,830 ± 5068	21,603 ± 4965	0.231
Time to angina (sec)	298 ± 121	330 ± 105	0.169
Time to 1 mm ST depression (sec)	285 ± 152	329 ± 140	0.021
HRR at 1 minute at the 1st exercise testing (beats/min)	25 ± 10	30 ± 13	<0.001

HRR = heart rate recovery; ET = exercise test; RPP = rate-pressure product.

In addition to the significant modification of HRR for the total of the 128 patients, the percentage of them that was considered as high-risk group after each exercise testing, was proportionately modified, as it is shown in Figure 1. Using a cutoff value of 18 beats/min, which is considered more appropriate when a cool-down period is not used, there was a trend for statistical significance ($P = 0.051$).

Based on these first results, the study patients were divided in two groups in accordance to the modification of HRR. Patients with increased HRR at the second exercise testing compared to the first exercise testing comprised group I ($n = 88$). In contrary, patients with reduced or unchanged HRR comprised group II ($n = 40$). Between-group comparisons of baseline characteristics and angiographic data are also shown in Table 1. There was

no significant difference between the two groups, with the exception of a trend for higher prevalence of diabetic patients in group II ($P = 0.058$). Between-group comparisons of exercise parameters are presented in Table 3. There was no significant difference in exercise duration and maximum *RPP*. With regard to the ischemic threshold, *RPP* at 1 mm ST-segment depression was comparable for the two groups at the first exercise testing. Notably, at the second exercise testing, patients of group I had a significantly higher *RPP* at 1 mm ST-segment depression compared to patients of group II ($P < 0.046$). Thus, patients of group I showed a significant augmentation of their ischemic threshold, showing a favorable adaptation to exercise-induced ischemia, while patients of group II showed a slightly reduced ischemic threshold ($P < 0.001$).

As it is also shown in Table 3, patients of group I had a significantly lower HRR at the first exercise testing compared to patients of group II ($P = 0.007$). However, they presented a significant increase of 9.6 ± 8 beats/min, compared to a reduction of 4.9 ± 4 beats/min of group II patients ($P < 0.001$). As a result, HRR of group I patients at the second exercise testing was found significantly higher than that of group II patients ($P < 0.001$).

DISCUSSION

In a model of sequential exercise testings, HRR was found to be significantly modified after a first positive exercise testing and this modification was associated with myocardial adaptation to exercise-induced myocardial ischemia. According to our results, a majority of patients with CAD, under certain exercise circumstances, are able to elicit a

Figure 1. Number of patients with reduced heart rate recovery (HRR) in relation to the HRR changes. ET = exercise testing.

Table 3. Between-group Comparisons of Exercise Parameters

	Group I (N = 88) (HRR Increased at the 2nd ET)	Group II (N = 40) (HRR Stable or Decreased)	P Value
Exercise duration at the 1st exercise testing (sec)	447 ± 137	462 ± 150	0.564
Exercise duration at the 2nd ET (sec)	476 ± 136	493 ± 131	0.523
Change of exercise duration (2nd vs 1st exercise testing) (sec)	30 ± 62	31 ± 86	0.923
Maximal ST depression (mm) at 1st exercise testing	2.37 ± 0.8	2.22 ± 0.7	0.307
Maximal ST depression (mm) at 2nd exercise testing	1.93 ± 1	2.21 ± 0.7	0.120
Maximum rate-pressure product at 1st exercise testing (mmHg/ min)	25,850 ± 4892	25,186 ± 4238	0.753
Maximum rate-pressure product at 2nd exercise testing (mmHg/min)	26,658 ± 4364	25,442 ± 3962	0.135
Change of maximum rate-pressure product (2nd vs 1st exercise testing) (mmHg/ min)	808 ± 3099	256 ± 2653	0.331
Rate-pressure product at 1 mm ST depression at the 1st exercise testing (mmHg/ min)	20,768 ± 4998	20,965 ± 5282	0.840
Rate-pressure product at 1 mm ST depression at the 2nd exercise testing (mmHg/ min)*	22,270 ± 4677	20,335 ± 5302	0.046
Time to angina at 1st exercise testing (sec)	277 ± 123	361 ± 93	0.027
Time to angina at 2nd exercise testing (sec)	329 ± 138	329 ± 146	0.999
Time to 1 mm ST depression at 1st exercise testing (sec)	274 ± 149	311 ± 158	0.199
HRR at 1 minute at the 1st exercise testing (beats/ min)	23 ± 10	28 ± 10	0.007
HRR at 1 minute at the 2nd exercise testing (beats/ min)	33 ± 13	23 ± 9	<0.001
Change of HRR at 1 minute (2nd vs 1st exercise testing) (beats/ min)	9.6 ± 8	-4.9 ± 4	<0.001

HRR = heart rate recovery; ET = exercise test.

cardioprotective anti-ischemic mechanism that is expressed as an enhancement of both ischemic tolerance and vagal tone and may be related to myocardial ischemic preconditioning mechanism.

HRR is an exercise parameter that has been associated with autonomic cardiac tone and decreased HRR has been correlated with increased mortality in patients with CAD.^{2,3,5} In clinical practice, HRR has been used as a prognostic tool and as such as a marker it should be accurate and reproducible. However, as it was postulated by our results, HRR after the second exercise testing showed a significant augmentation in comparison to the first.

Analyzing further the results, we also saw that beyond HRR, there were changes in other exercise parameters (maximal ST-segment depression, time to 1 mm ST-segment depression, and maximal exercise duration), while 12 patients (9.4% of the study population) had a negative second exercise testing and 10 patients (10.6% of those who presented angina) did not present angina during the second exercise testing. According to these results, one could hypothesize that HRR augmentation could be related to myocardial adaptation to ischemia process.

Although a correlation between HRR modification and myocardial adaptation to exercise-induced ischemia seemed intriguing, Table 2 shows initially no significant evidence of metabolic adaptation, since basically *RPP* at 1 mm ST depression, which is considered as an estimate of the ischemic threshold, did not change significantly from the first to the second exercise testing.

Based on a previous work of ours, where it was shown that almost two-thirds of patients with CAD can motivate adaptation to exercise-induced ischemia mechanism and improve their ischemic tolerance after repetitive exercise testings,¹⁰ and also on Maybaum and colleagues' report where it was reported that most but not all patients with CAD improve their ischemic tolerance after repetitive exercise,¹⁴ we tried to investigate whether this heterogeneous response was also encountered in this study. Accordingly, the study patients were retrospectively divided into two groups: group I comprised 88 patients who presented augmentation of the HRR in the first compared to the second exercise testing, while group II comprised 40 patients who presented unchanged or reduced HRR. After

between-group comparison of exercise parameters, it was found that patients of group I seemed to significantly improve their ischemic threshold (expressed as at the *RPP* 1 mm ST depression) in addition to the improvement of their HRR, while patients of group II did not improve or even worsened their ischemic threshold in addition to the worsening of their HRR. Thus, a parallel modification of HRR and ischemic threshold was found, relating an augmentation of vagal tone with myocardial adaptation to ischemia.

As it was abovementioned, in previous studies, using several models of exercise-induced myocardial ischemia, both a first and a second "window" of anti-ischemic protection have been recognized, which features a main characteristic of ischemic preconditioning mechanism.¹¹⁻¹⁴ Considering that in the present study the second exercise testing was performed after a 24-hour interval, it is likely that the results of this exercise testing have been influenced by the second-window of ischemic preconditioning, which had been triggered by the first exercise testing. Although the confounding role of a training effect cannot be entirely excluded, it is remarkable that between-group comparisons of exercise parameters showed a significant augmentation of ischemic threshold, revealing motivation of metabolic mechanisms, but not in maximal *RPP* and exercise duration, as it could be expected in the case of training effect.

Limitations of the Study

The major limitation of the study is the lack of convincing evidence, which could prove beyond any reasonable doubt that the first exercise-induced ischemic stimulus was capable to induce cardioprotection to all the studied patients. Thus, we could not possibly exclude that some of the group II patients would respond differently to sequential training if a more aggressive protocol during the first exercise testing was followed. However, such a protocol would neither be easily proved by the hospital's committee, nor would be easily followed by a relatively large number of unselected patients. Furthermore, the study participants stopped medical treatment before exercise depending on the half-life of the specific regimen. Response to repetitive undertreatment exercise may be different, since antianginal medications influence exercise performance, ischemic threshold, and myocardial adaptation to ischemia. The grouping of the study

participants was performed after the second exercise testings. Indeed, retrospective categorization could be considered a limitation of the study, but the variable response to sequential exercise training could not be predicted according to patients' baseline or angiographic characteristics or even the exercise parameters of the baseline exercise testing, as it was initially proposed in a previous study of ours.¹⁰

CONCLUSIONS

In a model of repetitive exercise testings in patients with CAD, a high test-retest variability of HRR was detected. This modification of HRR was correlated with respect to modification of the ischemic threshold, assessed by changes of the *RPP* at 1 mm ST-segment depression, raising an issue of a possible impact of adaptation to ischemia mechanism on autonomic tone. Further studies are warranted, aiming to delineate whether HRR changes after repetitive exercise testings is a direct result of autonomic tone modification and whether this phenomenon is part of the cardioprotective mechanisms related to myocardial adaptation to repetitive episodes of myocardial ischemia. However, accumulating data suggest that the clinical importance of ischemic preconditioning phenomena may be clinically exploited,^{15,16} resulting in improved outcome. In the light of these data the role of autonomic cardiac control on exercise-induced ischemic preconditioning phenomena should be further evaluated.

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