Mechanisms of the warm-up phenomenon

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The warm-up phenomenon, described in patients with coronary artery disease, refers to the improved performance following a first exercise test. The aim of this study was to investigate the causes of the warm-up phenomenon.

Fifteen patients with coronary artery disease and positive exercise test were enrolled. Patients were off treatment throughout the study. They underwent two consecutive treadmill exercise tests according to the Bruce protocol, with a recovery period of 10 min to re-establish baseline conditions. A third exercise test was then performed 2 h later. Before the onset of ischaemia, the rate-pressure product for a similar degree of workload was similar during the first and second exercise test, while it was lower during the third test (P<0.05). Time to 1-5 mm ST-segment depression during the second and third exercise test was greater than during the first test (454 ± 133 and 410 ± 161 vs 354 ± 127 s, P<0.01, respectively). Similarly, the time to anginal pain onset was increased during the second and third exercise tests, compared to the first test (356 ± 208 and 310 ± 203 vs 257 ± 204 s, P<0.01, respectively). In contrast, rate-pressure product at 1-5 mm ST-segment depression during the second test was higher than that during the first test (232 ± 47 vs 210 ± 39 beats·min⁻¹·mmHg·10⁻², P<0.01), while in the third test it was similar to that during the first (209 ± 43 beats·min⁻¹·mmHg·10⁻², P=ns).

The warm-up phenomenon observed a few minutes after exercise is characterized by an increase of both time to ischaemia and ischaemic threshold; this adaptation to ischaemia may be due to an improvement of myocardial perfusion or to preconditioning. Conversely, the warm-up phenomenon observed a few hours after repeated exercise is characterized by an increase of time to ischaemia but not of ischaemic threshold and is caused by a slower increase of cardiac workload. Thus, the mechanisms of the warm-up phenomenon may be different, time dependent and related to previous training.

(Eur Heart J 1996; 17: 1022-1027)

Key Words: Ischaemic preconditioning, myocardial ischaemia, training, warm-up phenomenon.

Introduction

The warm-up phenomenon, described in anginal patients more than 50 years ago[1,2], usually refers to the improved performance following a first exercise test[3-8]. However, the mechanisms underlying the warm-up phenomenon are still poorly known and somewhat controversial. Potential causes of the warm-up phenomenon are as follows: (1) an improvement of oxygen supply, which, in turn, may be caused by stenosis dilation, collateral recruitment or myocardial perfusion redistribution[3-6], (2) an adaptation to ischaemia, such as that caused by ischaemic preconditioning[7,8,10,11], and (3) a slower increase of cardiac workload, similar to that during training[12,13].

To shed some light on the causes of the warm-up phenomenon, we studied 15 patients with stable angina and documented coronary artery disease, who underwent two sequential treadmill exercise tests followed by a third test 2 h later.

Methods

Patients

Fifteen patients (13 men; two women; aged from 47 to 70 years, mean 61 years) with chronic stable angina pectoris (symptom duration ranging from 6 to 48 months), participated in this study. All patients had reproducible positive exercise tests for myocardial ischaemia with horizontal or downsloping ST-segment depression.


Previously presented as a preliminary report in abstract form (Eur Heart J 1995; 16 (Suppl): 499).

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0195-668X/96/071022+06 $18.00/0

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depression ≥ 2.0 mm. All patients had at least one critical stenosis (internal diameter reduction > 70% by visual assessment) in the proximal two-thirds of one major epicardial coronary artery. Coronary angiography showed one-vessel disease in six patients, two-vessel disease in five patients and three-vessel disease in four patients. All patients were normotensive, in sinus rhythm and without evidence of previous myocardial infarction, heart failure, cardiomyopathy or valvular disease. No patient had evidence of left ventricular hypertrophy or conduction defects which could interfere with the interpretation of ST-segment changes and no patient was taking digitalis. Nitrate preparations, other than sublingual nitroglycerin and calcium entry blocking agents, were withdrawn 4 days before the study and β-blocking agents 5 days before. Only sublingual nitroglycerin was used during the latter period and a minimum of 12 h were allowed to elapse before testing was begun if this drug was used. All patients gave written informed consent for participation in the study, which was approved by the Ethics Committee.

**Exercise test**

All patients underwent two consecutive, computer-assisted treadmill exercise tests, using the Bruce protocol, with a recovery period of 10 min between the tests to re-establish baseline electrocardiographic conditions. A third exercise test was then performed 2 h later, using the same protocol. All exercise tests were performed between 0900 and 1200 h with the laboratory temperature 22–24 °C. A standard 12-lead electrocardiogram and arterial blood pressure (cuff sphygmomanometer) were obtained in the standing position at baseline, at 1 min intervals during exercise, at peak exercise, and each minute up to 10 min after exercise as well as at 1-5 mm ST-segment depression, at the onset of angina, and when it was clinically indicated. Three electrocardiographic leads were continuously monitored before, during and after exercise, and up-to-date averaged QRS complexes of all electrocardiographic leads were continuously displayed on screen. The level of the ST-segment, 0.06 s after the J point, was calculated after signal averaging by means of a computer-assisted system (CASE Marquette 12) in all 12 leads. The calculated values were printed out, along with the heart rate, against time in trend format. This provided measurement of the ST-segment level with an accuracy of 0.1 mm.

Criteria for interrupting the test were: (1) ST-segment depression ≥ 3 mm; (2) maximal age-related heart rate; (3) severe chest pain; (4) physical exhaustion; and (5) the occurrence of other harmful conditions such as hypotension, severe arrhythmia, and dyspnoea. Myocardial ischaemia was diagnosed when a horizontal or downsloping ST-segment depression of 1-5 mm at 0.06 s from the J point was observed in at least one lead. The electrocardiographic strips of all tests were evaluated independently in a blind fashion by two cardiologists; in case of disagreement, the matter was resolved by consensus.

At the beginning of each exercise test patients were instructed to promptly report the onset of anginal pain. The following parameters were measured:

1. resting heart rate and blood pressure;
2. time, in seconds, to the onset of 1-5 mm ST-segment depression;
3. heart rate, blood pressure and rate–blood pressure product (heart rate × systolic blood pressure) at each minute of exercise up to peak exercise, and at the onset of 1-5 mm ST-segment depression;
4. maximal ST-segment depression;
5. metabolic equivalents of oxygen consumption at the onset of 1-5 mm ST-segment depression and at peak exercise;
6. exercise duration, in seconds;
7. time to the recovery of ST-segment depression, in seconds;
8. time to pain onset, in seconds.

**Statistical analysis**

One-way analysis of variance (ANOVA) for repeated measures was used to compare haemodynamic and electrocardiographic data during repeated exercise tests. When significant differences were detected, pairwise comparisons were made using the Scheffé F-test. Time to 1-5 mm ST-segment depression and to pain onset was analysed using the Friedman test, because these data did not fit to a normal distribution. Data are expressed as mean ± 1 SD, unless otherwise indicated. P<0.05 was considered significant.

**Results**

The main results of the three exercise tests are summarized in Table 1. All patients achieved 1-5 mm ST-segment depression during the three tests. At baseline, heart rate and rate–pressure product were slightly higher during the second than during the first and third exercise test (89 ± 11 vs 80 ± 13 and 82 ± 11 beats . min⁻¹, P<0.01; and 113 ± 26 vs 104 ± 25 and 105 ± 21 beats . min⁻¹ . mmHg . 10², P<0.05, respectively).

Before the onset of ischaemia, heart rate and rate–pressure product at a similar workload were similar during the first and second exercise test, while they were lower during the third test (at the end of the third minute, P<0.01 and P<0.05, respectively) (Fig. 1).

Time to 1-5 mm ST-segment depression during the second and third exercise test was greater than during the first test (454 ± 133 and 410 ± 161 vs 354 ± 127 s, P<0.01, respectively). Similarly, in the six patients who complained of anginal pain, the time to pain onset was increased during the second and third exercise test, compared to the first test (356 ± 208 and 310 ± 203 vs 257 ± 204 s, P<0.01, respectively) (Fig. 2).

In contrast rate–pressure product at 1-5 mm ST-segment depression during the second test was higher than
Table 1  Results of the three exercise stress tests in patient population

<table>
<thead>
<tr>
<th></th>
<th>Test 1</th>
<th>Test 2</th>
<th>Test 3</th>
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<tbody>
<tr>
<td><strong>Baseline values</strong></td>
<td></td>
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<tr>
<td>Heart rate (beats . min$^{-1}$)</td>
<td>80 ± 13</td>
<td>89 ± 11*</td>
<td>82 ± 11</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>132 ± 15</td>
<td>127 ± 18</td>
<td>129 ± 16</td>
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<tr>
<td>RPP (beats . min$^{-1}$ . mmHg . 10$^2$)</td>
<td>104 ± 25</td>
<td>113 ± 26†</td>
<td>105 ± 21</td>
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<tr>
<td><strong>Values at 1-5 mm ST depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats . min$^{-1}$)</td>
<td>131 ± 12</td>
<td>139 ± 15††</td>
<td>131 ± 15</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>159 ± 25</td>
<td>166 ± 25</td>
<td>160 ± 23</td>
</tr>
<tr>
<td>RPP (beats . min$^{-1}$ . mmHg . 10$^2$)</td>
<td>210 ± 39</td>
<td>232 ± 47*</td>
<td>209 ± 43</td>
</tr>
<tr>
<td>Time (s) (median values)</td>
<td>345 ± 127‡</td>
<td>454 ± 133</td>
<td>410 ± 161</td>
</tr>
<tr>
<td>Time to pain onset (s) (median values)</td>
<td>(333)</td>
<td>(480)</td>
<td>(391)</td>
</tr>
<tr>
<td><strong>Values at peak exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats . min$^{-1}$)</td>
<td>140 ± 14</td>
<td>149 ± 15*</td>
<td>140 ± 15</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>165 ± 27</td>
<td>172 ± 31</td>
<td>167 ± 28</td>
</tr>
<tr>
<td>RPP (beats . min$^{-1}$ . mmHg . 10$^2$)</td>
<td>233 ± 50</td>
<td>256 ± 57*</td>
<td>235 ± 53</td>
</tr>
<tr>
<td>Duration of exercise (s)</td>
<td>450 ± 149</td>
<td>531 ± 151*</td>
<td>458 ± 162</td>
</tr>
<tr>
<td>ST depression (mm)</td>
<td>2-4 ± 0-8</td>
<td>2-2 ± 0-7</td>
<td>2-4 ± 0-9</td>
</tr>
<tr>
<td>ST recovery (s)</td>
<td>505 ± 208</td>
<td>396 ± 138††</td>
<td>488 ± 230</td>
</tr>
<tr>
<td>METS</td>
<td>8-5 ± 2-5</td>
<td>9-9 ± 2-5‡‡</td>
<td>9-3 ± 2-9</td>
</tr>
</tbody>
</table>

Time to pain onset refers to the six patients with angina. BP = blood pressure; METS = metabolic equivalents; RPP = rate-pressure product.

*P < 0.01 vs test 1 and 3; †P < 0.05 vs test 1 and 3; ††P < 0.01 vs test 2 and 3; ‡P < 0.01 vs test 1.

Exercise tests, are: (1) an improvement of ischaemic threshold and of time to ischaemia during the second exercise test, performed within minutes of the first; (2) a loss of improvement in ischaemic threshold during the third test, performed 2 h after the second, with persistence of improvement of time to ischaemia; and (3) a slower increase of cardiac workload during the third exercise test. These findings taken together suggest that the warm-up phenomenon observed within minutes of a first exercise test is due to either improved myocardial perfusion or adaptation to ischaemia. Conversely, the warm-up phenomenon observed 2 h after the second exercise test, is due to a training effect caused by peripheral mechanisms. Thus, the mechanisms underlying the warm-up phenomenon are probably different, time-dependent and related to previous training.

**Assessment of the warm-up phenomenon**

Previous studies performed in patients with coronary artery disease undergoing consecutive stress tests have suggested that a variable proportion of these patients, ranging from 20 to 80%, tolerate the second period of ischaemia better than the first, i.e. they present a warm-up phenomenon. The marked variability of results in previous studies is probably due to the utilization of parameters such as the time to onset of angina, exercise duration and electrocardiographic variables at peak exercise, which are greatly influenced by the subjective attitude of both the physician and the patient. In

**Discussion**

The main findings of this study, carried out in patients with stable angina who underwent three consecutive exercise tests, are: (1) an improvement of ischaemic threshold and of time to ischaemia during the second exercise test, performed within minutes of the first; (2) a loss of improvement in ischaemic threshold during the third test, performed 2 h after the second, with persistence of improvement of time to ischaemia; and (3) a slower increase of cardiac workload during the third exercise test. These findings taken together suggest that the warm-up phenomenon observed within minutes of a first exercise test is due to either improved myocardial perfusion or adaptation to ischaemia. Conversely, the warm-up phenomenon observed 2 h after the second exercise test, is due to a training effect caused by peripheral mechanisms. Thus, the mechanisms underlying the warm-up phenomenon are probably different, time-dependent and related to previous training.
Warm-up phenomenon

Figure 1 Mean values of (a) heart rate and (b) rate-pressure product at the end of each minute during the first (□), second (●) and third (■) exercise test, before the onset of ischaemia. The increase of heart rate and rate-pressure product during the third test was consistently slower than that during the first and second test. Numbers in brackets indicate the number of patients who reached that minute of exercise. *P<0.05 (exercise test 3 vs 1 and 2); †P<0.01 (exercise test 2 vs 1 and 3).

Figure 2 Bars showing the median values of (a) time to 1.5 mm ST-segment depression and (b) to pain onset, during the first (□), second (●) and third (■) exercise test. *P<0.05 (exercise test 3 vs 1 and 2); †P<0.01 (exercise test 2 vs 1 and 3).

In this study, the results of exercise tests were compared using the heart rate and the rate-pressure product at 1.5 mm ST-segment depression, which represent objective, non-invasive indexes of the ischaemic threshold, i.e. of oxygen consumption at the onset to ischaemia, whereas the time to 1.5 mm ST-segment depression and to pain onset were considered as global indexes of exercise tolerance, which also take into account the peripheral response. Thus, in agreement with recent studies, we observed an improvement of more than 10% in the ischaemic threshold and in time to ischaemia in about 70 and 90%, respectively, of our patients during the second test, compared to the first.

Mechanisms of the warm-up phenomenon early after exercise-induced ischaemia

In this study, the improvement of ischaemic threshold observed during the second exercise test, performed within minutes of the first test, may be explained by an increase or a redistribution of myocardial perfusion, by adaptation to ischaemia, or by both mechanisms.

Williams et al. and Okazaki et al. have demonstrated in patients with a single lesion of the left anterior descending coronary artery that great cardiac vein flow was similar during the first and second stress test (exercise and atrial pacing, respectively), thus suggesting that the warm-up phenomenon was not accompanied by an increase in total myocardial blood flow.

Interestingly, Okazaki et al. found a relative reduction in myocardial oxygen consumption during the second test, thus suggesting that the warm-up phenomenon might have been caused by a mechanism similar to that involved in limiting experimental infarct size following a brief ischaemic episode, i.e. ischaemic preconditioning, which is also known to occur in humans. It is worth noting that in our study, the improvement of ischaemic threshold during the second test was lost after 2 h, despite the persistence of increased exercise tolerance. The time course of the ischaemic threshold observed in this study and in a recent study by Stewart et al. is consistent with that of ischaemic preconditioning. Indeed, in all tested animal species, the myocardial protection offered by ischaemic preconditioning lasts no longer than 60–90 min.

Finally, it cannot be excluded that our results, and those of Williams and Okazaki, might be due to myocardial blood flow redistribution or to a reduction of myocardial oxygen consumption secondary to the myocardial stunning induced by the first exercise.
Mechanisms of the warm-up phenomenon late after exercise-induced ischaemia

Another interesting finding of this study was the persistent increase of time to ischaemia during the third test, performed 2 h after the second test, despite loss of the improvement of the ischaemic threshold. This apparent paradox was due to the slower increase in heart rate and rate-pressure product during the third test, compared to that during the first and second tests. It would appear, therefore, that the improvement of exercise capacity observed in our patients during the third test was due to a training effect, resulting in a reduction of the cardiac workload. Although it has been reported that the peripheral haemodynamic changes associated with the training effect are observed only after weeks or months\(^\text{[12,13,28]}\), in this study they were already apparent during the third test, probably because of a quicker familiarization of the patients with the procedure and the staff.

Limitations of the study

A limitation of the study is that the rate-pressure product at 1.5 mm ST-segment depression was used as a surrogate for myocardial oxygen consumption at the onset of ischaemia. However, several studies have shown that the rate-pressure product, a simple parameter to obtain in the clinical setting, is a reliable index of myocardial oxygen consumption, particularly in the same patient\(^\text{[12,14]}\). Another limitation of our study is the assessment of blood pressure during exercise by sphygmomanometer, which is not always reliable. However, there is abundant evidence that the main determinant of myocardial oxygen consumption during dynamic exercise is heart rate\(^\text{[14,29,30]}\). Our results based on the assessment solely of heart rate are sufficient to support the conclusions of our study. Thus, the noise introduced by measuring blood pressure during exercise should decrease the statistical power of the study rather than create false-positive results.

References

