What Induces the Warm-Up Ischemia/Angina Phenomenon: Exercise or Myocardial Ischemia?

Peter Bogaty, MD; Paul Poirier, MD, PhD; Luce Boyer, RN; Jean Jobin, PhD; Gilles R. Dagenais, MD

Background—The relation of the warm-up ischemia phenomenon to the presence and intensity of initial myocardial ischemia is unclear. We sought to determine whether the warm-up ischemia phenomenon requires initial myocardial ischemia or can be induced by exercise without ischemia and whether there is a relation between the intensity of initial ischemia and the attenuation of ischemia on reexercise.

Methods and Results—Twelve subjects with exertional myocardial ischemia performed 2 exercise ECG tests (1 and 2) at a ±10-minute interval on 3 occasions (A, B, C) 1 month apart. A1 and A2 were symptom-limited. B1 was kept as long as A1, but its intensity was held under the ischemic threshold (heart rate × systolic pressure at 1-mm ST depression [STD]) noted at A1. B2 was symptom-limited. C1 was also kept as long as A1 but with an intensity adjusted to maintain one-half maximum STD of A1. C2 was symptom-limited. Exercise duration of A2, B2, and C2 increased similarly compared with A1 (P = 0.009). However, the ischemic threshold (× 10⁻³) increased at A2 (23.5 ± 6.0) compared with A1 (20.3 ± 4.8; P < 0.0001) but not at B2 (19.8 ± 5.0) or C2 (21.5 ± 5.8). Similarly, maximum STD adjusted to the highest heart rate–systolic pressure product common to A1, A2, B2, and C2 decreased at A2 (1.4 ± 0.7 mm) compared with A1 (2.5 ± 0.9 mm; P < 0.0001) but not at B2 (2.7 ± 0.9 mm) or C2 (2.3 ± 0.9 mm).

Conclusions—Exercises under the ischemic threshold and of intermediate ischemic intensity increase short-term exercise capacity, but myocardial ischemia of more than moderate intensity is needed to induce the warm-up ischemia phenomenon. (Circulation. 2003;107:1858-1863.)

Key Words: ischemia • heart diseases • exercise • angina

Warm-up angina is a common and intriguing phenomenon in which, in subjects with ischemic heart disease, angina induced by initial exercise is attenuated or even disappears if they briefly slacken or interrupt their exertion before resuming it at the same or even greater level of intensity.¹⁻³ Warm-up ischemia can be objectively demonstrated as a significant decrease in ECG signs of myocardial ischemia on the second of two exercise tests performed within a short interval.⁴⁻⁶ The mechanism of this important attenuation of myocardial ischemia remains undefined. It has been likened to ischemic preconditioning whereby, in animal models, brief intermittent coronary artery occlusions can substantially reduce myocardial infarct size when the coronary artery is subsequently occluded for a longer time.⁷ However, contrary to the latter phenomenon, warm-up ischemia does not seem to be mediated by adenosine or by cardiac adenosine triphosphate–sensitive potassium channels.⁶,⁸ It also is unexplained by a downregulation of contractile function or an increase in collateral myocardial perfusion induced by initial exercise.⁶,⁸

It would be relevant to know the intensity of exercise and/or myocardial ischemia that induces the optimal attenuation of myocardial ischemia on subsequent exercise. Such findings could have important implications for the prescription of exercise in subjects with ischemic heart disease. The purpose of this study was first, to determine whether the conditioning stimulus necessary to attenuate subsequent exercise-induced myocardial ischemia could be exercise itself without superimposed myocardial ischemia or whether indeed myocardial ischemia is required. Second, it was to determine the relation between the intensity of the initial conditioning ischemic stimulus and the degree of attenuation of myocardial ischemia on subsequent exercise.

Methods

Patients

Twelve subjects participated in this study. They were required to have (1) stable angiographically documented coronary artery disease (≥ 60% stenosis); (2) a resting ECG without ST-segment deviation ≥ 0.5 mm of the isoelectric line and without left ventricular hypertrophy or ventricular conduction abnormality; (3) a previous positive ECG exercise test (≥ 1 mm horizontal or downsloping ST-segment depression [STD] 80 ms after the J point in comparison to the baseline tracing at rest) with positivity occurring at least one exercise stage before the end of exercise. All subjects had a history of exertional angina and had previously performed several reproducible exercise tests and were familiar with this procedure. The hospital ethics committee approved the study, and all patients gave written, informed consent.
Study Design

Three exercise test sessions were held 1 month apart to render a training effect highly unlikely. A schema of the study design is shown in Figure 1. The first session (A) was the baseline warm-up protocol. This involved 2 successive exercise tests (A1 and A2) separated by an interval (intertest time) that depended on the subject’s willingness to reexercise and return of the ST segment to its original resting baseline. On the basis of previous work, this was found to be about 10 minutes.6,8 A1 and A2 were both symptom-limited. Symptom-limited was defined as the attainment of a discomfort score of 7/10 on an adapted visual Borg scale6 plus another 30 seconds for capture of peak exercise ECG and blood pressure data.6,8 At the second session (B), the first exercise (B1) was kept as long as A1, but its steady-state intensity (treadmill speed and gradient) was held at two thirds of the ischemic threshold (heart rate×systolic blood pressure product [RPP] at 1 mm STD) noted at A1. Thus, A1 was an ischemic exercise, and B1 was considered an exercise test without ischemia. B2 was a symptom-limited exercise. At the third session (C), the exercise intensity of C1 was modulated by adjusting treadmill gradient and speed to maintain 50% of maximum STD noted at A1, and its duration was kept the same as both A1 and B1. Thus, C1 was considered to be an ischemic stimulus of intermediate or moderate intensity. C2 was a symptom-limited exercise. Intertest times of A, B, and C were held 1 month apart. Intertest times (±10 minutes) were always the same for each subject.

Exercise Test Protocol

β-Blocking agents and calcium antagonists were stopped 72 hours and long-acting nitrates 12 hours before each exercise session. On the day of each session, subjects were instructed not to exercise, to avoid any unusual exertion, and to refrain from smoking, and they rested for at least 30 minutes before exercise testing, which was always undertaken in midafternoon at least 2 hours postprandially and was conditional on the absence of angina that same day before exercise testing. The modified Bruce protocol was used on a Q65 treadmill linked to a Q4000 monitor (Quinton Instrument Co). The ECG was continuously monitored. A standard 12-lead ECG was taken in the resting supine, sitting, and standing positions and then at least every 30 seconds during exercise and recovery, which was in the sitting position. Each time, both an averaged and a raw data ECG were obtained. Blood pressure was obtained with a mercury sphygmomanometer at least every 2 minutes during exercise, at 1-mm STD, and at peak exercise. The ECG display screen was shielded such that both subject and cardiologist were blinded to exercise duration. The same cardiologist supervised all tests.

Exercise Test Analysis

The exercise test was considered positive at first appearance of sustained 1-mm STD 80 ms after the J point, compared with the resting ECG taken in the sitting position just before exercise. All analyses were based on averaged tracings that were always compared with raw data and examined for consistency requiring 3 consecutive beats with the same findings. The symptom-limited exercises (A1, A2, B2, and C2) were compared. The control exercise was A1. Exercise duration and workload expressed as metabolic equivalent units, ischemic threshold, time of onset of exercise test positivity, time to onset of angina, RPP at appearance of angina (anginal threshold), peak RPP, and maximum STD were noted. Because peak RPP may vary from one exercise test to another, the adjusted maximum STD was analyzed. This measurement allows meaningful comparison of maximum STD among the exercise tests by adjusting for cardiac work as evaluated by RPP.6,8 It was determined by identifying the highest RPP achieved that was common to the exercises being compared and measuring the corresponding STD. STD recovery time was also noted. This was the time from end-exercise to the final appearance of 1-mm STD during postexercise rest in the sitting position. Because T-wave inversion often occurs during recovery and seems to drag down the ST segment, the latter was scrutinized, and if it rose during recovery to <1-mm depression only to subsequently drop down with T-wave inversion, this latter change was not considered as recovery time.10 Exercise tracings were analyzed independently by 2 examiners who were unaware of the place of each exercise in the study design. Differences were resolved by consensus.

Statistical Analysis

Values are expressed as mean±SD. A repeated-measures design was used to compare intrasession (A2 versus A1) and intersession exercise ECG parameters (B2 and C2 versus A1). A posteriori comparisons were performed with the use of Dunnett’s technique. Comparisons of RPPs during symptom-limited exercises were analyzed with Tukey’s method. Multivariate normality (Mardia test) and variance assumptions were fulfilled. The relations of ischemic indexes at A1 to the degree of attenuation of the ischemic threshold and adjusted maximum STD from A1 to A2 were evaluated by using Pearson’s correlation coefficients. A probability value of <0.05 was considered significant. Data were analyzed with the statistical package SAS (SAS Institute Inc).

Results

The 10 men and 2 women of this study were 63±7 years old. Six subjects had effort angina on a regular basis and the others had it less frequently. No patient changed his or her physical lifestyle during the study period. The number of diseased coronary vessels was 2.2±0.8 at angiography, performed 4±2 years previously. Left ventricular ejection fraction was 68±8% (range, 59% to 78%). One subject had a previous myocardial infarction, 6 had hypertension, 4 had type 2 diabetes, and no subject was a current smoker.

Intertest time at the 3 exercise sessions, determined for each subject at the A session, was 11±2 minutes (range, 8 to 15), comparable to previous studies demonstrating the warm-up phenomenon with successive exercise tests.5,6,8 Exercise test data are shown in Table 1 and Figure 2. Maximum STD at the initial “priming” exercise (A1) was 3.0±0.9 mm. Maximum STD at the initial exercise of intermediate ischemic intensity (C1) was 1.6±0.4 mm. None of the B1 exercises attained 1-mm STD. Despite the differing workload intensities of initial exercise, duration of the second exercise test increased similarly relative to the first test at the 3 sessions (P<0.0001). Time to onset of myocardial ischemia

Figure 1. Schema of study protocol. Sessions A, B, and C were held 1 month apart. Intertest times (±10 minutes) were always the same for each subject.
(1-mm STD) also increased significantly at all three second exercises compared with A1 ($P<0.0001$).

In contrast, the ischemic threshold of the second exercise at the 3 sessions increased only at A2 ($23\pm7.3\text{ min}$ compared with A1 ($Figure 2A$). Similarly, adjusted maximum STD decreased from $2.5\pm0.9$ mm at A1 to $1.4\pm0.7$ mm at A2 ($P<0.0001$), again demonstrating the warm-up ischemia effect, but did not change significantly either at B2 ($2.7\pm0.9$ mm) or at C2 ($2.3\pm0.9$) compared with A1 ($Figure 2B$). Compared with A1, recovery time was significantly decreased at A2 ($P=0.007$) but not at C2 nor at B2 ($Table 1$).

We looked for a relation between the intensity of ischemia (maximum STD) during symptom-limited A1 exercise and the degree of attenuation of myocardial ischemia as measured by the change of ischemic threshold or adjusted maximum STD from A1 to A2 ($Table 2$). If there were such a direct relation, it would suggest that more induction of myocardial ischemia on initial exercise leads to more attenuation of ischemia on reexercise. Such a correlation was not found ($Table 2$). This suggests that once there is an ischemic stimulus of sufficient intensity at initial exercise to attenuate subsequent ischemia, a greater degree of myocardial ischemia at that initial exercise does not seem to induce less ischemia at reexercise. However, there was a trend to a moderate correlation between the duration of ischemia (time that STD decreased from 2.5 mm to 1 mm) at initial symptom-limited exercise and subsequent attenuation of myocardial ischemia on reexercise ($Figure 2B$).

Ten subjects had typical angina at A1 and also at A2, B2, and C2. No subject had angina at B1, and 6 of 12 subjects had angina at the intermediate ischemic intensity exercise, C1. The remaining 2 subjects had intense dyspnea, considered an angina equivalent, at all symptom-limited exercises. Time to typical angina was increased compared with A1 after all 3 priming exercises, whatever their intensity ($P=0.0006$; $Table 1$).

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Duration, min</th>
<th>METs</th>
<th>RPP rest ($\times10^{-3}$)</th>
<th>RPP max ($\times10^{-3}$)</th>
<th>Time to Angina, min</th>
<th>Time to 1-mm STD, min</th>
<th>Max STD, mm</th>
<th>Recovery Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>10.2±3.1</td>
<td>9.3±2.9</td>
<td>11.6±2.3</td>
<td>26.2±4.8</td>
<td>7.1±3.0</td>
<td>4.8±1.9</td>
<td>3.0±0.9</td>
<td>4.0±3.8</td>
</tr>
<tr>
<td>A2</td>
<td>11.2±2.3*</td>
<td>10.2±2.2</td>
<td>13.6±2.6</td>
<td>28.2±5.3</td>
<td>10.2±2.3†</td>
<td>7.3±1.6§</td>
<td>2.6±0.7</td>
<td>2.2±2.2</td>
</tr>
<tr>
<td>B1</td>
<td>10.2±3.1</td>
<td>2.3±0.6</td>
<td>11.1±2.2</td>
<td>15.8±3.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td>B2</td>
<td>10.9±2.6*</td>
<td>9.7±2.5</td>
<td>10.9±2.4</td>
<td>25.6±3.9</td>
<td>8.8±2.6†</td>
<td>6.1±2.6§</td>
<td>2.9±1.0</td>
<td>3.8±3.3</td>
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<tr>
<td>C1</td>
<td>10.2±3.1</td>
<td>6.3±2.1</td>
<td>11.3±2.2</td>
<td>20.5±4.8</td>
<td>8.8±2.3‡</td>
<td>7.3±2.7‡</td>
<td>1.6±0.4</td>
<td>1.1±1.3</td>
</tr>
<tr>
<td>C2</td>
<td>11.5±2.3*</td>
<td>10.2±2.2</td>
<td>12.6±3.2</td>
<td>26.2±5.1</td>
<td>9.6±3.5†</td>
<td>7.7±2.1§</td>
<td>2.5±0.9</td>
<td>2.8±2.7</td>
</tr>
</tbody>
</table>

**Figure 2.** Ischemic threshold (A), adjusted maximum STD (B), and angina threshold (C) of symptom-limited exercises A1, A2, B2, and C2.
TABLE 2. Correlations Between Indexes of Intensity of Myocardial Ischemia at Initial Symptom-Limited Exercise (A1) and Degree of Attenuation of Ischemia With Reexercise (A2)

<table>
<thead>
<tr>
<th>Ischemic Intensity Indexes</th>
<th>% Change in Ischemic Threshold From A1 to A2</th>
<th>% Change of Adjusted Max STD from A1 to A2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max STD (A1)</td>
<td>$r = -0.04; P = 0.9$</td>
<td>$r = 0.11; P = 0.7$</td>
</tr>
<tr>
<td>Duration of exercise ischemia (STD ≥1 mm) at A1</td>
<td>$r = 0.51; P = 0.1$</td>
<td>$r = 0.46; P = 0.1$</td>
</tr>
</tbody>
</table>

Max STD indicates maximum ST-segment depression.

A1, A2, B2, and C2 (Figure 3). Compared with A1, RPP at A2 tended to be higher at baseline and during exercise ($P = 0.08$). Thus, the attenuation of myocardial ischemia and later onset of angina and STD at A2, despite its higher RPP, reflect a true warm-up angina and warm-up ischemia effect independent of cardiac work. On the other hand, the later onset of angina and of 1-mm STD at B2 and C2 compared with A1 can be attributed to a slower progression of their RPPs compared with A1 ($P = 0.03$). Angina occurred at all symptom-limited exercises 2.0 to 2.9 minutes after the onset of 1-mm STD except for 2 subjects at 2 exercise sessions, when angina and ischemia occurred within 30 seconds of each other.

**Discussion**

This study determined that whereas mild exercise without detectable cardiac ischemia increased exercise duration, time to ischemia, and time to angina, it failed to induce an attenuation of more rigorous ECG indicators of myocardial ischemia on subsequent exercise. Exercise of greater intensity that provokes moderate myocardial ischemia similarly improved exercise performance and time to ischemia and angina but also failed to attenuate these indicators of myocardial ischemia on reexercise. However, when initial exercise was symptom-limited and produced greater myocardial ischemia, a reduction in myocardial ischemia was observed with reexercise. Thus, the attenuation of ischemia on reexercise seems to require a priming or conditioning stimulus of myocardial ischemia and not merely exercise, and this ischemic stimulus must be of more than intermediate intensity to be effective. In addition, the absence of a relation between the intensity of exercise-induced myocardial ischemia at A1 as evaluated by STD and the degree of ischemic attenuation at A2 raises the possibility that above the threshold of induction, the conditioning ischemic stimulus is an “all or none” phenomenon. However, this study suggests that a relation may exist between ischemic time during initial symptom-limited exercise and subsequent attenuation of myocardial ischemia with immediate reexercise.

Interestingly, angina was consistently and significantly postponed on reexercise even when the initial priming exercise was well under the ischemic threshold. However, a more rigorous index that attempts to control for cardiac work or myocardial oxygen consumption, the angina threshold (RPP at onset of angina), only increased significantly on reexercise after a maximum ischemic initial exercise, consistent with the findings for the ischemic threshold and adjusted maximum STD (Figure 2). Thus, in contrast to these latter three indexes that only improved after an initial symptom-limited ischemic exercise, time to onset of angina (as well as time to STD) improved after even mild initial exercise without ischemia. This disassociation between ischemia and angina can probably be explained by the dynamics of heart rate and arterial blood pressure, which were less reactive on reexercise if the initial exercise was of mild (B1) or moderate (C1) intensity. The lower baseline and slower increases in RPP on reexercises B2 and C2, compared with A1, had the effect of postponing the onset of ischemia (1-mm STD) and angina (Figure 3). In this regard, there is a warm-up *angina* effect even when there is no detectable myocardial ischemia on initial exercise. This is also consistent with patients’ descriptions of a warm-up effect in everyday life after even mild exercise. The observations of this study thus highlight and account for the apparent paradox that although initial mild nonischemic exercise suffices to create a warm-up angina effect through a favorable short-term influence on myocardial oxygen demand during subsequent exercise, the attenuation of myocardial ischemia on reexercise, independent of cardiac work, requires a priming exercise of sufficient ischemic intensity. The observation that sufficiently intense (ie, symptom-limited) initial exercise seems necessary to drive up RPP on reexercise to a higher plateau (as evidenced by the RPP plot of A2 compared with A1 in Figure 3) is consistent with findings in previous studies in which the RPP at
reexercise was higher both at rest and at peak exercise when the initial exercise was symptom-limited.6,8,11

Previous Work
To our knowledge, the only other study that has specifically examined this question is that of Kay et al,12 who investigated the effects on ischemic reexercise of 3 warm-up protocols of differing intensities. Their “slow” protocol (treadmill exercise at 2.7 km/h for 20 minutes with no gradient) was identical for all subjects and was designed to avoid myocardial ischemia. These authors found that “submaximal” STD, which was maximum STD normalized to the longest exercise duration common to all exercises analyzed, decreased on reexercise after their slow protocol compared with no warm-up. Exercise duration did not increase on reexercise after slow warm-up, in contrast to our finding. Ischemic threshold and maximum STD at equivalent RPP were not examined. In contrast to their study, our nonischemic protocol was specifically adapted to each subject’s ischemic threshold. Thus, it is unclear from these authors’ findings whether exercise under the ischemic threshold can attenuate myocardial ischemia. Their other 2 protocols had the same ultimate workload but differed in duration and rate of acceleration. The more intense protocol seemed to attenuate ischemia on reexercise to a greater degree. In contrast, our intermediate exercise was specifically tailored to attain about half the ischemia achieved with maximum exercise, and this level was unable to induce an attenuation of myocardial ischemia.

Limitations
Although the study group was not large, the number of exercise tests analyzed was robust and results were consistent. The study group was also homogeneous in its principal baseline clinical characteristics. Such patient selection was necessary to properly evaluate mechanisms in warm-up angina, and findings might not necessarily apply to all patients with angina. Findings on a modified Bruce treadmill test might also not necessarily be extrapolated to other exercise protocols or to physical activities of daily life, although we and others have described the warm-up myocardial ischemia phenomenon by using different exercise protocols and intensities.3–6,8 We do not know the optimal intertest time for attenuating myocardial ischemia. Stewart et al4 have found that the warm-up effect was considerably decreased with a 30-minute rest compared with a rest period of 10 minutes. The comparative effect of a rest period <10 minutes on ischemic attenuation is not known, although its ECG interpretation could be problematic because the ST segment often has not yet returned to its resting baseline. Finally, we cannot exclude the possibility that it is moderate to strenuous exercise rather than intense ischemia per se that is responsible for the attenuation of myocardial ischemia on reexercise, because it is impossible to separate their effects in subjects who have exercise-induced myocardial ischemia.

Implications
Our findings have relevant implications and suggest a promising avenue for future research. Subjects with stable angina are usually advised to engage in regular exercise but to remain under their ischemic threshold. This is in accordance with traditional and current guidelines.13,14 Although this study was not designed or intended to explore the safety of exercise above the ischemic threshold, it does raise the provocative possibility that exercise that induces myocardial ischemia of greater than intermediate intensity may favor improved myocardial performance in subjects with ischemic heart disease. Previous small studies have shown that moderate to intense exercise training in patients with ischemic heart disease may raise the ischemic threshold and decrease maximum STD despite an increased peak exercise RPP.15,16 Although it has been suggested in a canine model of chronic coronary artery narrowing that vigorous exercise training can stimulate coronary collateral development,17 studies in humans with myocardial perfusion scintigraphy and angiography have failed to clearly support such findings.18–21 These studies may have been limited by technical inadequacies and failure to explore the effects of exercise of sufficient ischemic intensity. Another mechanism that might account for exercise-induced attenuation of myocardial ischemia is an improvement in endothelial function leading to increased coronary arterial reserve.22 By demonstrating that symptom-limited exercise associated with relatively important myocardial ischemia is required to attenuate subsequent exercise-induced myocardial ischemia, our study does not rule out a mechanism based on improved perfusion but raises the possibility that yet-undefined, metabolically mediated processes may account for this phenomenon. Larger and longer-term studies are warranted to examine the safety and repercussions of this singular, apparently adaptive mechanism that attenuates exercise-induced myocardial ischemia.

References


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