Exercise-Induced Myocardial Ischemia in a Cold Environment

Effect of Antianginal Medications

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The influence of cold on the threshold for myocardial ischemia and the efficacy of antianginal drugs in a cold environment were assessed in 24 patients with stable angina and exercise-induced ST depression. Treadmill exercise tests were done according to a randomized double-blind protocol 90 minutes after administration of placebo, 80 mg propranolol, or 120 mg diltiazem, each at both −8° and 20° C. Eight of the patients were classified by history as cold-sensitive before the study. For the entire group, none of the exercise end points differed significantly between cold and normal temperatures with placebo. However, cold-sensitive patients developed 1 mm ST depression 30% sooner (169±41 versus 244±38 seconds, p<0.01) at −8° C compared with 20° C. At the onset of ischemia, rate-pressure product was lower in the cold (19.8±1.0 versus 22.0±1.6×10^3, p<0.05). Both propranolol and diltiazem prolonged time to onset of 1 mm ST depression at both temperatures. The magnitude of improvement at −8° C was equal to that at 20° C, and differences between the two drugs were not statistically significant. Only diltiazem prolonged total exercise duration. Thus, as assessed by exercise testing, cold does not worsen ischemic threshold in most stable angina patients. However, in a subgroup identifiable by history, ischemic threshold is lower in the cold. Propranolol and diltiazem are as effective for exercise-induced ischemia in a cold environment as at normal temperatures. (Circulation 1989;79:1015–1020)

Many patients with angina report that their symptoms are worse in cold weather. The mechanism accounting for this phenomenon is controversial. During exercise testing, angina has been reported to occur earlier in a cold environment but at a similar rate-pressure product as at normal temperatures.1-3 This finding implies that an increase in myocardial oxygen demand, due to a cold-induced increase in peripheral vascular resistance,1 causes the cold-related reduction in exercise tolerance.

On the other hand, the cold pressor test induces vasoconstriction of atherosclerotic coronary arteries and an increase in coronary vascular resistance.4,5 Cold can provoke frank coronary spasm in patients with variant angina.6-7 Thus, a cold-induced aggravation of angina could also be caused by coronary vasoconstriction or the absence of normal coronary vasodilation during exercise.

β-Adrenergic-blocking drugs potentiate the coronary vasoconstriction induced at the site of atherosclerotic lesions by the cold pressor test.8,9 In contrast, nifedipine blocks this response.10 The efficacy of antianginal drugs has not been assessed in a cold environment.

This study was conducted to compare the ischemic threshold of patients with stable effort angina at cold and normal temperatures. Rate-pressure products at the onset of ischemia were compared between the two temperatures. Exercise testing was also done at both cold and normal temperatures after propranolol and after diltiazem.

Methods

Patients

The initial study group consisted of 28 patients with long-term stable angina pectoris. All patients in this group had documented coronary artery disease defined as 1) coronary stenoses of 70% or more of the lumen diameter at arteriography, 2) previously documented transmural myocardial infarction

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(elevated cardiac isoenzymes and Minnesota code electrocardiographic criteria\textsuperscript{11,12}, or 3) a reversible perfusion deficit on thallium exercise testing. All patients had both angina and 1 mm or more ST segment depression compared with baseline during standard exercise testing using the Bruce protocol. Exercise reproducibility was confirmed by two baseline tests that demonstrated less than 20% variability in exercise time to 1 mm ST segment depression.

Excluded were patients with myocardial infarction, unstable angina, or coronary bypass surgery within 3 months, overt heart failure, uncontrolled hypertension, serious arrhythmias, or baseline electrocardiographic abnormalities that could interfere with the interpretation of ST segment changes during exercise; patients requiring digitalis or antiarrhythmic or antianginal medications other than sublingual nitroglycerin; and patients with known contraindications to \( \beta \)-blockers or diltiazem. Three patients did not complete the study— one had worsening angina, one had nonsustained ventricular tachycardia during exercise, and one did not complete for personal reasons. One other patient who had poor quality electrocardiographic tracings was also excluded from analysis.

Thus, the final study group consisted of 22 men and two women with a mean age of 57 years (range, 37–72 years) and a mean duration of angina of 5.2 years; 23 were in Canadian Cardiovascular Society angina class II and one patient was in angina class III. Nine patients had had a previous myocardial infarction, and five had previously undergone bypass surgery. The effect of cold weather on angina was not used as a selection criterion. However, before study entry, all patients completed a questionnaire relating to their angina symptoms. Eight were classified as cold sensitive because they reported that their angina was definitely worse in the cold; the other 16 noted no such relation.

\textbf{Study protocol.} The study design was double-blind, randomized, and placebo controlled. Its purpose was to compare the effect of cold temperature (\(-8^\circ \mathrm{C}\)) with that of normal room temperature (\(20^\circ \mathrm{C}\)) on exercise test parameters either with no active medication, after 80 mg propranolol, or after 120 mg diltiazem. For each patient, three treadmill tests were performed at \(-8^\circ \mathrm{C}\), one with placebo, one with propranolol, and one with diltiazem; three treadmill tests were also performed at \(20^\circ \mathrm{C}\), also with placebo, propranolol, and diltiazem. The sequence of the six treadmill tests was randomized. All tests were performed 90 minutes after oral drug or placebo administration. For each patient, the two baseline tests and the six exercise tests in the study were completed within 3 weeks, with an interval of at least 48 hours between tests. All patients gave written, informed consent, and the study protocol was approved by our hospital Ethics Committee.

\textbf{Treadmill tests.} Treadmill exercise using a Bruce protocol was performed at approximately the same hour each day, with the patient fasting or at least 2 hours after a light meal. Heart rate, cuff blood pressure, and perceived exertion were recorded before and at minute intervals during exercise and recovery. Electrocardiographic leads CM\(_2\), CC\(_3\), and C\(_1\) were continuously monitored, and a complete electrocardiogram was recorded every 30 seconds to determine as precisely as possible the onset of 1 or more mm ST segment depression. The ST segment was measured 0.08 seconds after the J point in three consecutive QRS complexes with a flat baseline and R waves of equal amplitude. The average of the three measurements was compared with the baseline tracing, as previously described.\textsuperscript{13} Time to 1 mm ST segment depression, time to angina, total exercise duration, maximum ST segment depression, and rate-pressure product at each of these points were compiled. End points for terminating exercise were severe angina, dyspnea, or extreme fatigue.

A cold chamber was used to perform treadmill tests at \(-8^\circ \mathrm{C}\). This specially designed room (Foster Co, Canada) measured 12\(\times\)10\(\times\)8.5 ft. and maintained a constant temperature during treadmill tests. A ventilation system recycled the air, and a large window allowed constant supervision by staff operating the electronic equipment, which was kept at room temperature outside the cold chamber. Only the patient, the nurse who recorded blood pressure, and the treadmill (Quinton Instruments, Model 1854, Seattle, Washington) were placed inside the cold chamber; regular calibration showed that it was not affected by the cold temperature. Verbal communication with the patient and nurse inside the chamber was possible through an intercom system. All patients wore standardized clothing, a T-shirt and light pants, for the tests at \(-8^\circ \mathrm{C}\). Patients were allowed to complete the recovery period at normal room temperature. The treadmill tests at \(20^\circ \mathrm{C}\) were performed with the same equipment, properly calibrated.

\textbf{Statistical analysis.} One-factor ANOVA for repeated measures was used to compare exercise test parameters during the placebo tests (Table 2) and under the six different experimental conditions (Tables 1 and 3). When the overall F ratio was significant, Sheffé’s test was used to compare the means.\textsuperscript{14} This statistical approach is conservative; however, the use of a paired t test would not have produced a significant p value for any of the important comparisons that were not statistically significant. Total exercise duration was substituted for time to angina or time to 1 or more mm ST segment depression when these end points did not occur.

\textbf{Results}

\textbf{Effect of Temperature on All Patients}

As shown in Table 1, exercise test results were similar at \(-8^\circ \mathrm{C}\) compared with \(20^\circ \mathrm{C}\) for the 24 study patients who received placebo. Time to 1 mm ST segment depression (222±30 versus 252±22
Table 1. Exercise Test Data for All Study Patients

<table>
<thead>
<tr>
<th>Time to onset</th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST ≥1 mm (sec)</td>
<td>-8°C</td>
<td>+20°C</td>
<td>-8°C</td>
</tr>
<tr>
<td></td>
<td>222±30</td>
<td>252±22</td>
<td>320±19*</td>
</tr>
<tr>
<td></td>
<td>306±23</td>
<td>313±25</td>
<td>343±19</td>
</tr>
<tr>
<td></td>
<td>396±19</td>
<td>381±18</td>
<td>380±13</td>
</tr>
<tr>
<td>Total exercise duration (sec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At onset of 1 mm ST depression</td>
<td>Heart rate</td>
<td>126±3</td>
<td>129±3</td>
</tr>
<tr>
<td></td>
<td>Systolic pressure</td>
<td>171±5</td>
<td>175±5</td>
</tr>
<tr>
<td></td>
<td>Rate-pressure product (×10⁻³)</td>
<td>22.1±1</td>
<td>22.6±0.9</td>
</tr>
<tr>
<td></td>
<td>Maximal ST depression (mm)</td>
<td>2.1±0.2</td>
<td>2.1±0.2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n=24.
*tp<0.01 compared with placebo; †tp<0.01 compared with other drug; ‡lp<0.01 compared with placebo; †lp<0.05 compared with 20°C; ∥lp<0.05 compared with other drug.

seconds), rate-pressure product at 1 mm ST segment depression (22±1 versus 23±0.9×10⁻³), time to angina (306±23 versus 313±25 seconds), total exercise duration (396±19 versus 381±18 seconds), and maximal ST segment depression (2.1±0.2 versus 2.1±0.2 mm) were not significantly different.

At rest and after 1 minute of exercise, rate-pressure product was significantly higher in the cold compared with normal temperature, as shown in Table 2. This difference was due to a higher systolic pressure. By 3 minutes of exercise, rate-pressure products were similar at the two temperatures and remained so through the rest of the tests. Diastolic arterial pressure was slightly but significantly lower at -8°C compared with 20°C after 3 minutes of exercise, at 1 mm ST depression, and at maximal exercise.

Effects of Propranolol and Diltiazem

Both propranolol and diltiazem improved time to 1 mm ST segment depression at -8°C and 20°C compared with placebo, as shown in Table 1. The magnitude of improvement was similar with both drugs at both temperatures (propranolol, 98 seconds at -8°C and 89 seconds at 20°C; diltiazem, 82 seconds at -8°C and 87 seconds at 20°C). Compared with placebo, diltiazem improved time to angina and total exercise duration; this improvement was similar at both temperatures. Propranolol did not significantly improve time to angina at either temperature, and total exercise duration at both temperatures was slightly, but not significantly, less with propranolol compared with placebo. Total exercise duration at both temperatures was longer with diltiazem compared with propranolol (p<0.01).

Rate-pressure product at 1 mm ST depression was lower with propranolol at -8°C compared with 20°C. This difference was due almost entirely to a lower systolic pressure (151±5 versus 163±3, p<0.05) in the cold. Rate-pressure product at the onset of ischemia was similar at the two temperatures with diltiazem. At normal temperature, but not in the cold, patients exercised to a higher rate-pressure product with diltiazem than with placebo (p<0.05).

Maximal ST segment depression was less with propranolol and diltiazem compared with placebo and was less with propranolol than diltiazem. For both drugs, more ST depression occurred at -8°C than at 20°C.

Cold-Sensitive Patients

Eight of the 24 patients were classified as cold sensitive on the basis of the angina questionnaire they completed before study entry. As shown in Table 3, time to onset of 1 mm ST segment depression in this

Table 2. Heart Rate and Arterial Pressure Data During Placebo Tests for All Study Patients

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Rest</th>
<th>1 min</th>
<th>3 min</th>
<th>↓ ST</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>-8</td>
<td>87±3</td>
<td>108±2</td>
<td>117±3</td>
<td>126±3</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>85±2</td>
<td>107±2</td>
<td>115±3</td>
<td>123±3</td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>-8</td>
<td>144±5</td>
<td>152±4*</td>
<td>166±4</td>
<td>171±5</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>134±2</td>
<td>140±3</td>
<td>164±4</td>
<td>175±5</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>-8</td>
<td>82±2</td>
<td>80±2</td>
<td>81±2*</td>
<td>82±2*</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>82±1</td>
<td>80±1</td>
<td>86±2</td>
<td>88±2</td>
</tr>
<tr>
<td>Rate-pressure product (×10⁻³)</td>
<td>-8</td>
<td>12.5±0.5*</td>
<td>16.5±0.6*</td>
<td>19.5±0.7</td>
<td>21.5±1.0</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>11.4±0.4</td>
<td>15.0±0.4</td>
<td>19.0±0.7</td>
<td>22.6±0.9</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n=24.
*p<0.05 compared with 20°C.
group was 169±41 seconds at −8°C and 244±38 seconds at 20°C (p<0.01). This difference of 75 seconds represents a 30% decrease in time to onset of ischemia in the cold. No difference was noted in the other 16 patients who were not cold sensitive by history. In the cold-sensitive group, rate-pressure product at 1 mm ST segment depression was lower at −8°C than at 20°C (19.3±0.8 versus 22.0±1.6, p<0.05). This difference was also not present in the other group. Overall exercise duration and maximal ST segment depression were similar at −8°C compared with 20°C, as shown in Table 3.

**Propranolol and Diltiazem in Cold-Sensitive Patients**

Both propranolol and diltiazem significantly improved time to onset of 1 mm ST segment depression at both −8°C and 20°C, as shown in Table 3. The mean improvement was 143 seconds for propranolol (p<0.01) and 93 seconds for diltiazem (p<0.01) at −8°C and 105 seconds for propranolol (p<0.01) and 63 seconds for diltiazem (p<0.01) at 20°C. Differences between the drugs for time to 1 mm ST segment depression were not statistically significant. These results are similar to the findings in the entire group. Rate-pressure product at 1 mm ST segment depression was significantly lower at −8°C compared to 20°C for each of the pairs of tests: placebo, propranolol, and diltiazem, as shown in Table 3.

Maximal ST segment depression was less with propranolol than with placebo and diltiazem at both temperatures. There was no difference in maximal ST depression at −8°C compared with 20°C with either propranolol or diltiazem (Table 3).

**Discussion**

The results of the present study show that a cold environment does not reduce the duration of exercise or the time to the onset of ischemia overall in patients with stable angina. However, for the one third of the patients who reported that cold worsened their angina, time to 1 mm ST segment depression was significantly reduced at −8°C compared with 20°C by approximately 30%. In this subgroup, rate-pressure product at the onset of ischemia was significantly lower at −8°C than at normal temperature, implying that ischemia may be occurring at a lower myocardial oxygen consumption. Although this measurement is indirect, it suggests that less coronary flow may be reaching the ischemic zone during exercise in the cold.

**Previous Studies**

In 1934, Wayne and Graybiel reported that exercise tolerance was not reduced at low temperatures in six patients with effort angina. Epstein et al. studied six patients with coronary disease and found that exercise at 15°C induced angina at workloads that did not cause angina at 25°C. Cooling increased peripheral vascular resistance and arterial pressure. Lassvik et al. in 17 patients whose angina was worsened by cold, found that maximal workload with bicycle exercise was reduced by 7% at −10°C compared with 20°C. Heart rate, systolic arterial pressure, and rate-pressure product were significantly higher in the cold at submaximal exercise but at the onset of angina and at peak workload did not differ from the results at normal temperature. Our finding of a lower rate-pressure product at the onset of ischemia in cold-sensitive patients was not observed by Lassvik et al. This discrepancy may be due to differences in patient characteristics or methodology; for example, Lassvik et al reported data at the onset of angina, not the onset of ST depression.

Our patients began exercise within 1 minute after entering the cold chamber, because we had previously observed that a longer delay induced shivering and submaximal exercise performance for noncardiac reasons. Their rate-pressure products and systolic arterial pressures were higher at the start of exercise compared with the values at normal temperature; however, this difference disappeared dur-
ing exercise. A longer period of exposure to cold before the beginning of exercise, as done in some studies,\textsuperscript{1,15} may have provoked a more pronounced pressor response. Both situations are probably comparable to different conditions faced by angina patients during real life.

Studies with the cold pressor test are not comparable to studies with exercise in a cold environment. De Servi et al\textsuperscript{16} demonstrated that exercise abolishes the abnormal increase in coronary resistance induced by the cold pressor test in patients with coronary disease. Regional coronary flow and resistance were similar during exercise coincident with and without a cold pressor test. Lassvik et al\textsuperscript{3} demonstrated that both the inhalation of cold air and cutaneous stimulation contribute to the effect of cold on exercise tolerance.

After 3 minutes of exercise, at the onset of ischemia, and at maximal exercise, diastolic arterial pressure was slightly but statistically significantly lower in cold compared with that at normal temperature. Cold exposure at rest increases diastolic pressure,\textsuperscript{15} but diastolic pressures during exercise in the cold have not been reported in most studies.\textsuperscript{1-3,15} A lower coronary perfusion pressure could theoretically account for an earlier onset of ischemia at cold temperatures.

**Effect of Antianginal Drugs**

Propranolol augments the coronary vasoconstrictive response elicited in coronary patients by the cold pressor test.\textsuperscript{8,9} Theoretically, diltiazem might be expected to be a better antianginal drug in a cold environment because it is a coronary vasodilator, in contrast to propranolol. In this study, both propranolol and diltiazem delayed the onset of ischemia during exercise at both $-8^\circ$ and $20^\circ$ C. This beneficial effect at normal temperatures is quantitatively similar to results of previous studies.\textsuperscript{17} The antianginal efficacy of these drugs has not been investigated at low temperatures. The degree of improvement in time to onset of ischemia was similar with both drugs, at both temperatures, and in both cold-sensitive patients and the entire group. Diltiazem increased the total duration of exercise at both temperatures but propranolol did not.

The rate-pressure product at the onset of ischemia was similar at both temperatures with diltiazem but significantly lower with propranolol in the cold. This finding is compatible with more coronary vasoconstriction (or less vasodilatation) with propranolol at $-8^\circ$ C compared with normal temperature. Despite this, exercise time to the onset of ischemia improved with propranolol in the cold as at normal temperature because systolic arterial pressure was lower.

In the cold-sensitive patients, the rate-pressure product at the onset of ischemia was lower in the cold compared with normal temperature for diltiazem as well as with placebo and propranolol.

**Limitations of the Study**

A major limitation of this study is that rate-pressure product is an inaccurate and indirect method of assessing myocardial oxygen consumption. Other factors, such as wall tension and contractility, that contribute to myocardial oxygen consumption are difficult to measure during exercise testing and are ignored. The correlation between rate-pressure product and myocardial oxygen consumption has not been studied in humans under conditions of varying temperature and may be poorer than has been found in more narrowly controlled conditions. Cuff blood pressure measurements made at 1-minute intervals during exercise lack precision.

A second limitation involves the extrapolation of the results of this study to clinical situations. Transient ST depression, often without angina, frequently occurs during Holter electrocardiographic monitoring in patients with stable angina at heart rates much lower than those attained during exercise testing.\textsuperscript{18,19} The mechanisms provoking myocardial ischemia during daily life may not be the same as during exercise testing. Shea et al\textsuperscript{20} have demonstrated that cold pressor stimulation induces abnormal regional myocardial perfusion, usually without angina or ST depression, in most patients with stable angina. These abnormalities occur at rate-pressure products below the ischemic threshold during exercise testing, implying that they are caused by a reduction in coronary flow.

Third, the conditions of this study do not reproduce those faced by the patient with angina in real life. Wind, snow, and the weight of winter clothing would be expected to reduce exercise capacity. Holter monitoring could provide useful information relating to the ability of coronary patients to adapt to winter conditions.

**Clinical Implications**

In a minority of patients with stable angina, exercise in a cold environment reduces the threshold for myocardial ischemia. Indirect evidence from the present study suggests that this reduction is more likely to be due to an increase in coronary tone than to an increase in the determinants of myocardial oxygen consumption, at least under these conditions. Why only some angina patients react in this manner is not readily apparent. The danger of exposure to cold in patients with stable angina appears to be minimal.

Both diltiazem and propranolol delay the onset of exercise-induced ischemia to the same extent in the cold as at normal temperatures. Whether these drugs would be equally efficacious in preventing spontaneous angina episodes in the cold is not known. In addition to its theoretic advantage of being a coronary vasodilator, diltiazem prolonged total exercise duration in the study patients, whereas propranolol did not.
References


KEY WORDS • angina • diltiazem • propranolol
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