Exercise Performance and Electrocardiographic Changes as Indices of Effect of Long-acting Nitrates in Angina Pectoris

A. M. ABRAHAMSEN,* M.D., and F. KII.,† M.D.


Evaluations of anti-anginal drugs are usually based on electrocardiographic changes observed after a standard exercise test. Since there is little correlation between angina and electrocardiographic evidence of myocardial ischaemia (Katz, 1935; Russek et al., 1955), the conclusion is often drawn that anginal pain is a poor criterion of the effect of a drug in improving myocardial ischaemia (Russek, 1955; Sandler et al., 1963). This is obviously true for drugs acting on pathways of pain transmission. Alcohol, sedatives, tranquilizers, and monoamine oxidase inhibitors may favourably influence angina without electrocardiographic improvement (Russek et al., 1950, 1955). On the other hand, the validity of the electrocardiographic method in identifying effective agents, such as glyceryl trinitrate, is based on the observation that such drugs increase the exercise tolerance (Sandler et al., 1963, Russek and Howard, 1964). Angina and electrocardiographic changes may both reflect ischaemia in a minute area of the myocardium. The choice of method for evaluating less potent long-acting nitrates depends, therefore, on which method is most sensitive and reproducible when applied on a population with angina pectoris.

Most patients with coronary insufficiency believe that they are able to state quite exactly the onset of pain, and often develop pain in their daily life after the same amount of exercise. Whether this reflects coronary insufficiency at identical work loads or is due rather to a psychological reaction to the situation when pain is known to occur has not been settled. By using a Master two-step technique (Sandler et al., 1963) the patients may count the number of circuits accomplished. In the present study exercise was therefore performed on a bicycle ergometer. The ordinary controlled double-blind technique was modified in so far that the patients were told that the drugs had different potency and were likely to delay the onset of pain differently. This was done in order to minimize the placebo effect. The order of administration was of course kept secret. On three consecutive days one hour before exercise a placebo tablet or one of two long-acting nitrates (pentaerythritol tetranoitrate and methylpropranololidinitrate) was administered according to a permutation scheme (Kil, 1960). Methylpropranololidinitrate is synthesized by Apothekernes Laboratorium for Specialpaarater, Oslo, and marketed as Nitril.

Summary

The feasibility and efficiency of a standard administration scheme have been explored, using experience gained from previous experiments and clinical trials with streptokinase (S.K.) as a thrombolytic agent in man. With a set initial dose of 1,250,000 U. S.K. administered intra-arterially or intravenously in less than 30 minutes and a maintenance dose of 100,000 U. S.K./hour for three days, restoration of arterial blood-flow was obtained in 12 of 15 arterial occlusions.

REFERENCES

Method and Material

Twenty-four patients with precordial pain that radiated to one or both arms under strenuous activity were selected for this study. All had had a stable weekly consumption of glyceryl trinitrate for several months before the study. Two patients were excluded because of lack of co-operation and four others became heavily dyspnoeic during the exercise test. The study group was therefore composed of 18 patients—16 men and two women aged 46 to 66 years (average age 55 years). Angina pectoris had been present for one to eight years (average 3.5 years). Six patients had been hospitalized seven to 16 months previously because of well-authenticated myocardial infarction, and five of these showed electrocardiographic changes of an old infarction. The resting electrocardiogram was normal in seven of the 12 patients constituting the angina pectoris group without previous infarction. None of the patients included in this study had overt signs of heart insufficiency and they all tolerated the exercise tests without becoming severely dyspnoeic.

The exercise studies were performed in the morning on three consecutive days three to four hours after the previous meal. Tablets containing 8 mg. of nitroglycerin or a placebo tablet were swallowed 60 minutes before exercise, so that the drugs were given in all permutations to the six patients with previous myocardial infarction. This scheme was also followed for the 12 patients in the angina pectoris group without previous myocardial infarction. The drugs were called A, B, C and their identity was not revealed to the leader of the exercise tests (A. M. A.) until the results for all patients were collected. All exercise tests were performed on an Elema bicycle ergometer and none of the patients had any difficulty in keeping the frequency of pedalling constant. A work load of 300–800 kpm./min. was chosen after a preliminary trial and kept constant for each patient throughout the study. Exercise time was measured with a stop-waatch until the patient reported initial anginal pain, and the exercise was then stopped. Before and immediately after each test 12-lead electrocardiograms were obtained.

Results

Electrocardiographic changes when precordial pain was present were most consistent in chest leads, especially V₅ and V₆ (see Table). STV₅ changes measured to the nearest half-millimeter are shown in the last column of the Table. Only two of the six patients with previous infarction developed ST-

Sequence of Administration of Drugs, Work Performances, and ST-changes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sex</th>
<th>Order of Treatment</th>
<th>Work Load (kpm./min.)</th>
<th>Exercise Time (sec.)</th>
<th>STV₅ Changes (mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris with previous infarction</td>
<td>M</td>
<td>ABC</td>
<td>300</td>
<td>103</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>BCA</td>
<td>300</td>
<td>131</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>CAB</td>
<td>300</td>
<td>115</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>300</td>
<td>149</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>A</td>
<td>300</td>
<td>132</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>B</td>
<td>300</td>
<td>129</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>C</td>
<td>300</td>
<td>148</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>R</td>
<td>300</td>
<td>142</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>A</td>
<td>300</td>
<td>138</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>B</td>
<td>300</td>
<td>143</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>C</td>
<td>300</td>
<td>129</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>300</td>
<td>149</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>A</td>
<td>300</td>
<td>132</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>B</td>
<td>300</td>
<td>129</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>C</td>
<td>300</td>
<td>148</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>R</td>
<td>300</td>
<td>142</td>
<td>0</td>
</tr>
</tbody>
</table>

Means of daily exercise times:

<table>
<thead>
<tr>
<th>Means of exercise time after medications</th>
<th>A, B, C</th>
</tr>
</thead>
<tbody>
<tr>
<td>122.9</td>
<td>128.4</td>
</tr>
<tr>
<td>117.5</td>
<td>120.7</td>
</tr>
</tbody>
</table>

A slightly higher correlation (0.91) was obtained when the exercise times after the administration of methylpropylpropanediolinitrate and placebo were compared. In Fig. 2 the stippled line is fitted by the method of least squares. It runs parallel (b=0.97) to the solid line of equal response. The exercise time was on average 21.8 seconds longer after treatment with methylpropylpropanediolinitrate. This difference was found to be significant (P<0.02) and corresponds to an increase in exercise time of 18%.
Since the figures might suggest that the material is not normally distributed, Wilcoxon's non-parametric ranking test was also used, and confirmed that the exercise time was significantly longer after the administration of methylproppypropandioldinitrate than after placebo (P<0.05). This was also found when the response after methylproppypropandioldinitrate was compared with individual mean responses of the two other drugs.

Discussion

ST-changes are recorded in 50-60% of patients with a definite history of angina pectoris and with normal resting electrocardiograms after a standard exercise test (Davis et al., 1953; Gazes et al., 1964). In the present study, where all post-exercise recordings were obtained during precordial pain, STV, changes occurred in seven out of 18 patients, whereas nine patients showed ST-changes when all leads were taken into account. Though ST-changes were observed in only two of six patients with previous myocardial infarction, it might be argued that patients with precordial pain without electrocardiographic changes did not suffer from coronary insufficiency. Exclusion of these patients does not, however, render the effect of methylproppypropandioldinitrate and pentaerythritolpropandioldinitrate more favourable.

The electrocardiographic response varied with treatment in five patients, and in four of these the smallest ST-changes occurred after pentaerythritol-propandioldinitrate (see Table). Selection of these patients for further study might well confirm that pentaerythritol-propandioldinitrate has a beneficial influence on ST-changes, as previously found by Russek and Funk (1962). However, the criterion of benefit should be relief of anginal pain and not decrease in degree of electrocardiographic abnormality or the extent of coronary dilatation. We found no relationship between exercise time and electrocardiographic changes, and it is doubtful if ST-changes reflect myocardial blood supply either absolute or relative to metabolic demand:

1. The characteristics of the input capacitors of the clinical electrocardiographs prevent a discrimination between ST-segment shifts and base-line shifts. The latter may occur, for instance, during tachycardias and make the interpretation "extremely complicated" (Schaefer and Haas, 1962).

2. Severe acute disturbances of myocardial blood flow and electrical activity in dogs may be induced without changes of the epicardial electrocardiogram (Sayen et al., 1961).

3. The large variability between local myocardial flow, measured by hydrogen polarography (Aukland et al., 1964), and ST-changes would invalidate any attempts to quantitate ischaemia even by intramyocardial recordings (Aukland, unpublished studies).

Though anginal pain is considered unreliable as a quantitative measure of coronary insufficiency (Russek, 1955), detailed studies have been lacking. Sandler et al. (1963) used a Master two-step test and found that their patients with and without placebo treatment accomplished on average 44.7 and 43.9 circuits respectively until pain or dyspnoea prevented further exercise. From their data we calculated a correlation coefficient of 0.89, which corresponds well with those obtained in the present study (0.91-0.83) by comparing the performances on different days.

In a bicycle ergometer test, where the work load is adjustable so that pain develops suddenly after a few minutes' exercise, initial pain should be the end point. One should not depend on the decision of the patient when to stop exerting himself, since this is likely to reduce the sensitivity of the test and increase the hazard. Patients with severe dyspnoea should be excluded, since onset of dyspnoea is gradual and reflects myocardial insufficiency only in a very indirect way.

Mathisen and Holen (1962) showed in a long-term study that methylproppypropandioldinitrate had a better glyceryl trinitrate sparing effect than placebo, whereas recent studies have shown that pentaerythritol tetranitrate is without effect (Oram and Sowton, 1961; Cole et al., 1963). The effect of long-acting nitro-esters must be considerable compared with glyceryl trinitrate in order further to reduce a low and regular consumption of glyceryl trinitrate. Sandler et al. (1963) found that 1 mg. glyceryl trinitrate administered sublingually immediately before a Master two-step test increased the number of circuits accomplished from 43.9 to 63.7 (mean response of 15 patients). This corresponds to an increase in work performance of 45%, whereas 8 mg. methylproppypropandioldinitrate in the present study increased the work performance by 18%. Though these studies are not strictly comparable, they suggest that methylproppypropandioldinitrate has an effect which is definitely lower than that of glyceryl trinitrate, but that methylproppypropandioldinitrate is a useful adjunct in the treatment of angina pectoris.

Summary

Eighteen patients with typical angina pectoris with or without electrocardiographic abnormality performed exercise on a bicycle ergometer after receiving long-acting nitrates (pentaerythritol tetranitrate and methylproppypropandioldinitrate) or placebo tablets according to a permutation scheme. Exercise time until onset of pain was found to be highly reproducible and the technique sensitive enough to measure an increase in exercise time of 18% after methylproppypropandioldinitrate, whereas pentaerythritol tetranitrate had no significant effect.

Nine of the 18 patients, including four of six with previous myocardial infarction, did not develop ST-changes and there was no relationship between degree of ST-changes and exercise time. This study suggests that exercise time is a better criterion than electrocardiographic changes in the quantitative evaluation of anti-anginal drugs.

References


