Late exercise test results from a prospective randomized study of bypass surgery for stable angina

GEORGE A. PANTELY, M.D., FRANK E. KLOSTER, M.D., AND CYNTHIA D. MORRIS, M.P.H.

ABSTRACT A prospective randomized study comparing coronary bypass surgery (group 1, 51 patients) to drug therapy (group 2, 49 patients) was initiated in 1981. Supine graded exercise testing (SGXT) was performed initially, at 6 months, and annually with a bicycle ergometer. The presence or absence of ischemic ST segment changes (positive or negative SGXT) and chest pain were recorded. Initially, 63% of all patients had positive SGXT. For group 2, the frequency of positive SGXT results did not change significantly at 6 months (58%) or at 5 years (52%). At 6 months the number of patients without chest pain increased in group 1 compared with group 2 (28/41 vs 13/41, respectively; p < .002), but there was no difference in the frequency of positive SGXT results (20/41 vs 24/41, respectively; p = NS). This occurred because a majority of the group 1 patients with positive SGXT no longer had associated chest pain (group 1, 11/20, group 2, 3/24; p < .007). This response was associated with incomplete revascularization in eight of these 11 group 1 patients and may result from "silent ischemia." At 5 years, no significant difference existed in the incidence of positive SGXT (group 1, 10/32 vs group 2, 12/23; p = NS), but group 1 patients continued to have a reduction (although not statistically significant) in the number of patients without chest pain (group 1, 19/32 vs group 2, 7/23). The incidences of death and myocardial infarction were not significantly different between groups. Fewer episodes of unstable angina occurred in group 1 (10/51 vs 19/49; p < .05). The prognosis of group 1 patients with positive SGXT and no chest pain and incomplete revascularization was not different from that of the entire group. *Circulation* 68, No. 2, 413-419, 1983.

A PROSPECTIVE randomized study comparingortocoronary saphenous vein bypass surgery to drug management in patients with stable angina was initiated at the Oregon Health Sciences University and the Portland Veterans Administration Hospital in 1971.1,2 All patients underwent supine graded maximum exercise testing (SGXT) at entrance into the study, approximately 6 months after entrance, and annually thereafter. In this article, we compare the results of the exercise tests in drug- and surgically treated patients after 5 years of follow-up studies. In addition, we evaluate a subgroup of surgically treated patients who had ischemic ST segment depression without associated chest pain during the postoperative exercise tests to determine the etiology and significance of that response.

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Methods

Details of the trial have been described previously.1,2 Candidates for the trial had disabling angina pectoris (functional class III or IV despite therapy) for at least 1 year, were 62 years of age or younger, had no episodes of unstable angina or myocardial infarction within 6 months, had no clinical evidence of heart failure or cardiomegaly, and had no other major disabling illnesses. After 5 years, 100 patients were enrolled, 51 in the surgical treatment group (group 1) and 49 in the drug treatment group (group 2).

All patients underwent coronary and left ventricular angiography and SGXT. Coronary angiography was performed by the Judkins technique.3 The results were evaluated independently by two observers, and any differences were reconciled by concordance. If one or more major coronary arteries had more than 50% reduction in luminal diameter and the distal vessel was suitable for grafting, the patient was randomly assigned to drug or surgical therapy. Patients with left main coronary artery disease were excluded.

SGXT was performed with a bicycle ergometer. Exercise was initiated at a low workload, usually 200 kilopond-meters, and increased in 200 kpm increments at 3 min intervals, with a brief rest between exercise periods, until the patient was unable to continue because of dyspnea, fatigue, or chest pain. Interrupted exercise was used because it provides a more precise determination of heart rate and systolic blood pressure product at the threshold of angina.4,5 Exercise was stopped by the physician if serious cardiac arrhythmias developed. Almost all patients had
stopped taking propranolol and nitroglycerin 24 hr before their initial and 6 month tests; however, only about half of the patients had stopped taking these medications before the 5 year test. The electrocardiogram (ECG) (lead CM3) was monitored continuously and was recorded at the end of each level of exercise and at intervals during the recovery period. Horizontal or downsloping segmental ST segment depression of 1 mm or more and lasting 0.08 sec or of 1.5 mm and lasting 0.08 sec if the ST segment was upsloping were required for interpretation as a positive exercise test. The occurrence of chest pain during the stress test was recorded. Coronary angiography was repeated at 6 months and approximately 5 years after entrance into the study. Exercise stress tests were performed at 6 months after entry and annually thereafter.

Major clinical events were tabulated for each group, including death, myocardial infarction, and unstable angina. Unstable angina was defined as prolonged episodes of pain at rest or a pattern of increasing frequency or severity of pain. Patients with unstable angina were treated with bed rest, oxygen, sedation, analgesia, propranolol, and nitrates and were considered candidates for surgery if unstable angina persisted despite drug therapy.

Statistical analysis. Comparison of initial and follow-up studies for continuous variables in individual patients were analyzed by Student's t test, and population differences for categorical variables were tested by the chi-square method. Results are expressed as mean ± SEM.

Results

Patients. Characteristics of the patient groups at the time of entry into the study are shown in table 1. The age, sex distribution, functional class, occurrence of prior myocardial infarction, resting ECG abnormalities, distribution of coronary artery disease, and ejection fraction were not significantly different between the groups. The presence of Q waves in appropriate leads or enzyme and ECG documentation were required for diagnosis of a previous myocardial infarction.

Exercise stress tests. The results of initial, 6 months, and 5 year SGXT for group 1 (surgically treated) and group 2 (drug-treated) are shown in Figure 1. The results do not include patients whose data were incomplete, who died, or who had unstable angina requiring surgery. Patients who had a myocardial infarction and those with an episode of unstable angina that responded to drug treatment are included. During initial evaluation, 63% of both groups had a positive exercise test. Of those patients with a positive test, 88% of group 2 patients and 96% of group 1 patients had associated chest pain. There was no correlation between resting ECG abnormalities (ST-T wave abnormalities and prior infarction) and the results of the initial SGXT.

At 6 months the results for group 2 had not significantly changed: 58% of the patients had a positive SGXT. The responses were consistent; 76% of the patients had a positive SGXT (by ST-T wave abnormalities) on both tests. The number of patients without chest pain increased significantly in group 1 (28/41 [68%] vs 13/41 [32%] in group 2; p = .002); however, there was no difference in the frequency of abnormal SGXT (20/41 [49%] in group 1 vs 24/41 [59%] in group 2; p = NS). This occurred because a majority of the group 1 patients with positive exercise test results no longer had associated chest pain (11/20 [55%] in group 1 vs 3/24 [12%] in group 2; p = .007).

At 5 years the proportion of patients with a positive SGXT in group 2 had decreased slightly to 52%, but this did not differ significantly from their initial results. The association between a positive SGXT and chest pain was still present at 5 years, with 10 of 12 (83%) group 2 patients with a positive SGXT having associated chest pain. Group 2 had a 32% prevalence of positive SGXT at 5 years, a significant reduction compared with the initial studies (p < .025).

There was no significant difference in the prevalence of positive SGXT between the two groups at 5 years. Group 1 continued to have a reduction (although not statistically significant) in number of patients without chest pain (19/32 [59%] in group 1 vs 7/23 [30%] in group 2; p = NS).

A small percentage of patients was taking propranolol at the time of their initial and 6 month tests. There was no significant difference between the two groups in the number of patients on propranolol at the initial and 6 month studies (table 2). At the 5 year study, more group 2 patients were taking propranolol (p < .05). There was no association between the exercise test results and the use of propranolol at the initial and 6 month studies, whereas at 5 years a greater number of group 2 patients with a positive test were taking propranolol.
propranolol (p < .01). There was no association between exercise test results (positive or negative) or the occurrence of chest pain with the use of propranolol.

The maximum workload and maximum heart rate achieved were higher initially in group 2 than in group 1 (table 3). At 6 months, group 2 patients had a modest but statistically significant decrease in workload (p < .02) and in maximum heart rate (p < .05). A significant increase in both maximum workload and heart rate occurred in group 1 patients (p < .01). At 5 years, the maximum workload and maximum heart rate during exercise in group 2 were not significantly different from the initial values. Patients in group 1 continued to achieve a maximum workload and heart rate that were significantly higher than initial values and similar to the results at 6 months. Because of the small increase (p = NS) in maximum workload of group 2 patients and the small decrease (p = NS) in maximum heart rate of group 1 patients, there was no significant difference in these variables between the two groups at 5 years.

As mentioned above, a positive exercise test was usually associated with chest pain in the initial studies — this was the case in 88% of positive tests in group 2 and 96% in group 2 (figure 1). This was still true in 88% of group 2 patients at 6 months and 83% at 5 years.

FIGURE 1. Results of SGTX in group 1 (top) and group 2 (bottom). Cross-hatched portion of each bar indicates percent of patients with positive SGXT and clear portion indicates those with negative SGXT. + CP = occurrence of chest pain; - CP = absence of chest pain. The number of patients in each category is indicated. See text for discussion of results.
years; however, only 45% of group 1 patients with a positive SGXT had associated chest pain at 6 months, which differed significantly from the results of group 2 (p = .007). Thus 11 (55%) group 1 patients with ischemic ST segment depression during exercise at 6 months had relief of angina. Initial clinical characteristics of these 11 patients were not significantly different from those of group 2 or the remainder of the group 1 patients. None of them had a perioperative myocardial infarction, as assessed by new Q waves on the ECG, and none was taking propranolol at the initial and 6 month exercise test studies. Nine of the 11 had a positive SGXT and associated chest pain initially, while one had chest pain and a negative SGXT and the other had no chest pain and a negative SGXT. These patients had increases in maximum workload (initial, 375 ± 48; 6 month, 633 ± 183 kpm; p < .01) and heart rate (initial, 103 ± 4; 6 month, 129 ± 4 beats/min; p < .01) that were similar to the results in the other group 1 patients shown in table 3.

The presence and severity of anginal chest pain reported by these 11 patients during daily activity 6 months after surgery was as follows: six patients reported exertional chest pain (two reported no improvement while four reported infrequent or rare episodes of pain); five patients did not have any chest pain during daily activity.

Table 4 shows the relationship between the results of the exercise test at 6 months and the success of revascularization in all patients who had a positive exercise test initially. Revascularization was considered successful if all significantly obstructed major arteries were bypassed and all grafts were patent at the 6 month study. If all major distal vessels could not be bypassed, or one or more grafts were occluded or had a greater than 90% diameter stenosis, revascularization was considered incomplete. When revascularization was incomplete, 89% of the patients with an initially positive SGXT had a positive SGXT after surgery. This was true for eight of nine patients in the subgroup with a positive SGXT without associated chest pain at 6 months after surgery (two did not have a positive SGXT initially). If revascularization was successful, only 18% of the patients with a positive SGXT initially had a positive SGXT after surgery. Thus a significant association exists between the success of revascularization and the results of the SGXT (p < .001).

**Major clinical events.** Table 5 shows the major clinical events for groups 1 and 2 and for the subgroup with a positive SGXT without chest pain at 6 months. The incidence of death and myocardial infarction were not significantly different between groups 1 and 2, and fewer episodes of unstable angina occurred in the sur-

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**TABLE 2**

<table>
<thead>
<tr>
<th>SGXT result</th>
<th>Initial</th>
<th>6 mo</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
</tr>
<tr>
<td>All + SGXT</td>
<td>1/24</td>
<td>0/25</td>
<td>0/20</td>
</tr>
<tr>
<td>− SGXT</td>
<td>0/14</td>
<td>0/15</td>
<td>1/21</td>
</tr>
<tr>
<td>Chest pain present</td>
<td>1/34</td>
<td>0/31</td>
<td>1/13</td>
</tr>
<tr>
<td>No chest pain</td>
<td>0/4</td>
<td>0/9</td>
<td>0/28</td>
</tr>
</tbody>
</table>

*For all values numerator represents the number of patients taking propranolol; denominator represents the total number of patients with the result listed.

Statistical comparisons: p < .05; *p < .01.

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**TABLE 3**

<table>
<thead>
<tr>
<th>SGXT results (mean ± SEM)</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum workload (kpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>389(31) b</td>
<td>529(44) b</td>
</tr>
<tr>
<td>6 mo</td>
<td>655(32) a</td>
<td>469(40) a</td>
</tr>
<tr>
<td>5 yr</td>
<td>665(35) a</td>
<td>584(49) a</td>
</tr>
<tr>
<td>Maximum heart rate (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>105(3) a</td>
<td>116(3) c</td>
</tr>
<tr>
<td>6 mo</td>
<td>120(3) a</td>
<td>107(3) a</td>
</tr>
<tr>
<td>5 yr</td>
<td>114(4) a</td>
<td>106(3) a</td>
</tr>
</tbody>
</table>

Statistically significant differences between adjacent values: *p < .01; "p < .02; "p < .05.

---

**TABLE 4**

<table>
<thead>
<tr>
<th>Relationship between success of revascularization and postoperative SGXT results in patients* with positive SGXT before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularization</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Successfulb</td>
</tr>
<tr>
<td>Incomplete</td>
</tr>
</tbody>
</table>

*Group 1 patients, n = 24; group 2 patients who underwent subsequent bypass graft surgery, n = 6.

bSuccessful revascularization was associated with a negative SGXT after surgery, while incomplete revascularization was associated with persistence of positive SGXT (p < .001).
THERAPY AND PREVENTION—CORONARY ARTERY DISEASE

TABLE 5
Clinical events

<table>
<thead>
<tr>
<th>Event</th>
<th>Group 1</th>
<th>Group 1 subgroup</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>6</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Group I</td>
<td>3</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Group II</td>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

*Positive SGXT without chest pain at 6 mo follow-up.
Sixteen of the 17 deaths were due to cardiac diseases.
Patients requiring bypass surgery.
 Patients responding to drug management.
*p < .05 group 1 vs group 2.
One patient had two episodes of unstable angina, the first treated with drug therapy and the second with surgery.

In the subgroup with a positive SGXT without chest pain at 6 months, the incidence of major clinical events and the reduction in episodes of unstable angina were similar to those of group 1 as a whole.

Discussion

SGXT results: groups 1 and 2. A positive SGXT and associated chest pain were present initially in most (63%) patients with histories of exertional chest pain and documented coronary artery disease. Group 2 had no change in positive SGXT results, associated chest pain, maximum workload, and maximum heart rate 6 months and 5 years after entry into the study. In contrast, in group 1 there was a significant reduction in the incidence of positive SGXT results and associated chest pain, and a substantial improvement in maximum workload and maximum heart rate at 6 months compared with preoperative values. These results are similar to those of the Houston VA Randomized Study and of other nonrandomized studies. Group 1 continued to show improved exercise capacity and lower incidence of angina at 5 years compared with initial values. These long-term results are similar to those reported recently by Weiner et al. in a retrospective study. They reported that 20 patients showed an initial decrease in the frequency of anginal symptoms and improvement in exercise performance after bypass surgery. At 5 years the decrease in frequency of anginal pain persisted, but the frequency of positive SGXT results no longer differed compared with the preoperative results.

SGXT results: group 1 vs group 2. When compared with group 2 at 5 years, group 1 had maintained its lower incidence of angina noted at 6 months. However, in contrast to the 6 month results, no difference was present at 5 years in the frequency of abnormal SGXT or the maximum heart rate and workload achieved. This was due to slight, but not statistically significant, changes in each group. The number of patients who died or had a myocardial infarction was similar in both groups. Thus the extended benefits in group 1 patients were a lower incidence of chest pain during SGXT and fewer episodes of unstable angina.

Propranolol and SGXT results. Some patients performed their exercise tests while taking propranolol, despite our plans to avoid this, especially at the 5 year study. Some patients forgot to stop taking the propranolol 24 hr before study or refused to stop because their angina became worse. Two groups have shown that β-blockers had no effect on ST-T depression during exercise testing in patients with coronary artery disease. Our data show that the results of exercise testing (ST segment depression or the number of patients who experienced pain) were not affected by the use of propranolol in some patients.

Discrepancy between objective and subjective signs of ischemia after surgery. A positive SGXT was almost always associated with chest pain in the initial studies. This was still the pattern in group 2 patients at 6 months. However, after surgery, 60% of group 1 patients with a positive SGXT no longer had associated chest pain, a significant change compared with group 2. Almost all of these patients had a positive SGXT with chest pain initially.

Others have described a similar group of patients after bypass graft surgery. Mnayer et al. reported that 13 surgical patients (59% of the group) had ST depression without angina; this response occurred in only 9% (3/35) of drug-treated patients. Bartel et al. reported that 56% (19/34 patients) continued to have a positive exercise test after surgery but no longer had chest pain. Berndt et al. found that 33% of patients that had exercise testing after surgery for unstable angina no longer had chest pain but had a positive exercise test. None of these patients had preoperative exercise tests because of the unstable angina.

The mechanism underlying the absence of angina despite ischemic ST segment depression on an exercise test is unclear. This response is seen most commonly after bypass graft surgery, but the role the surgery plays in “causing” this response is not understood. Suggested mechanisms include (1) perioperative infarction of ischemic tissue, (2) placebo effect of surgery, and (3) denervation of ischemic areas.

Analysis of our patients with a positive SGXT and no chest pain after surgery indicated that none of the variables shown in Table 1 differed significantly from
those of group 2 or the remainder of the group 1 patients. They had improved exercise capacity after surgery and none of them had a perioperative infarction. The one significant finding we noted was that nine of these 11 patients had incomplete revascularization. This suggests that the ST depression noted during SGXT may have been caused by ischemia. Seven of these 11 patients reported having some episodes of chest pain during daily activities, indicating that total cardiac denervation due to surgery was not the reason for the absence of chest pain during SGXT.

Lindsey and Cohn\(^9\) speculated that these patients may have some episodes of "silent" myocardial ischemia, and there is evidence to support this suggestion. Ambulatory and bedside ECG monitoring suggests that episodes of myocardial ischemia (defined by ST segment depression) are not always accompanied by angina pectoris. Shang and Pepine\(^20\) studied 20 patients with coronary artery disease proven by coronary angiography. Each patient had ST segment depression during exercise testing with chest pain. Through almost 3000 hr of ambulatory monitoring, they identified 411 episodes of ST segment depression; only 25% of these episodes were accompanied by angina pectoris.

We do not know why chest pain does not occur during some episodes of ischemia. Maseri\(^21\) reported that in patients with rest angina, the pain usually followed the onset of ST segment changes. Upton et al.\(^22\) have reported on the late occurrence of angina compared with ST segment changes during exercise. In a preliminary report, Chierchia et al.\(^23\) found that symptomatic episodes of ischemia were longer than asymptomatic episodes and were associated with more severe left ventricular dysfunction. These reports suggest that during ischemia not accompanied by chest pain, the severity of ischemia may be less marked, the area or mass of myocardium involved may be less extensive, or both, than in myocardial ischemia associated with pain. It may be that in the patients with a positive SGXT without chest pain the surgery, although it was not completely successful, reduced the area or severity of ischemia, or both, so that chest pain did not occur with the amount of work done during the SGXT but would probably occur with more severe exertion. Radiouclide studies might indicate whether ischemia was present during exertion, but these techniques were not available at the beginning of our trial. Since this response (positive SGXT without chest pain) is associated with bypass graft surgery, it is possible that placebo effect, denervation of ischemic areas, or perioperative infarction play some role in the relief of pain.

The significance or risk of myocardial ischemia without chest pain is not clear. Patients who do not experience angina during myocardial ischemia may lack an important warning to stop an activity before there is potentially fatal damage to the myocardium or induction of arrhythmias.\(^7, 24\) Conversely, the prognosis of "silent" ischemia may not be worse than that of symptomatic ischemia.\(^25\) We have a small group of patients and firm conclusions are difficult to make, but their incidence of death (including sudden death) and myocardial infarction were not significantly different than those of group 2 and other group 1 patients. It is possible that important differences could not be detected between our groups because of a type II or beta error. With the sample sizes of 49 and 51 patients, a significance level of .05 and actuarial curve analysis, we have calculated that a difference of 7% per year between the two groups over a 5 year period for each major clinical event would be detected with a power of 0.90, that is, there is a 10% chance that such a difference could be missed. For differences of 6% and 5% per year, the discriminatory powers are 0.80 and 0.70, respectively. When smaller subgroups are considered, such as those patients with continued positive SGXT but loss of chest pain, the discriminating power becomes weaker and the probability of a type II error greater. For this reason, one must be cautious in interpreting the "nonsignificant" results in this study, particularly in subgroups of patients.

In summary, SGXT results showed that our surgically treated group had a significant decrease in the number of patients with a positive SGXT and in the number with chest pain, and a significant increase in work capacity up to 5 years after surgery, compared with preoperative results. When the results from the surgically treated group were compared with those of the drug-treated group at 5 years of follow-up, the surgically treated group had fewer episodes of unstable angina. There was no difference in the frequency of abnormal SGXT results, the frequency of chest pain during SGXT, the maximum heart rate and workload achieved, or in the incidence of death or myocardial infarction between the groups.

About half of patients that still had a positive SGXT after surgery no longer had associated chest pain. This response was associated with incomplete revascularization in 80% of these patients. The persistence of the positive SGXT is probably caused by myocardial ischemia; the absence of pain may indicate less severe myocardial ischemia than that associated with pain. Survival in these patients may not be different than that of drug- or other surgically treated patients.
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References


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