Prevalence and Prognostic Significance of Silent and Symptomatic Ischemia After Coronary Bypass Surgery: A Report From the Coronary Artery Surgery Study (CASS) Randomized Population

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The prevalence and prognostic significance of postoperative myocardial ischemia, as detected by exercise testing, were prospectively assessed in 174 patients from the Coronary Artery Surgery Study (CASS) randomized surgical population who had exercise testing before and 6 months after coronary artery bypass graft surgery. Whereas the prevalence of symptomatic ischemia significantly decreased postoperatively (52% vs. 6%, p < 0.001), the frequency of silent myocardial ischemia did not change (39% vs. 29%).

Survival at 12 years after bypass surgery based on the 6-month postoperative exercise test results was significantly better for the 112 patients with no ischemia (80%) than for the 51 patients with silent ischemia (68%) or the 11 patients with symptomatic ischemia (45%).

These data show that coronary artery bypass graft surgery diminishes the overall prevalence of symptomatic but not silent ischemia and that both silent and symptomatic ischemia adversely affect the postoperative prognosis of these patients.

(I Am Coll Cardiol 1991;18:343-8)

Methods

Study patients. The design, study protocol, procedures for randomization, quality control measures and baseline characteristics of the patients participating in CASS have been published previously (15). The CASS registry comprises 34,959 consecutive patients who underwent coronary arteriography at 14 cooperating clinical sites between 1974 and 1979. From this registry, 780 consenting patients with at least a 70% diameter stenosis of one or more operable vessels were randomly assigned to receive medical or surgical treatment at 11 participating sites. Clinical criteria for entry into the randomized trial included age ≥65 years and either angina of Canadian Cardiovascular Society class I or II or no symptoms with a well documented myocardial infarction ≥3 weeks before enrollment.

Data acquired pertinent to the present investigation included a standard medical history and physical examination, results of the enrollment cardiac catheterization and maximal exercise test results at baseline and at 6 months after randomization. All patients were prospectively fol-
followed up at yearly intervals to ascertain health status, with a minimum of 10 years of follow-up for each patient. Each patient enrolled at Boston University Medical Center signed an informed consent form approved by the Institutional Review Board at Boston University Medical Center on June 23, 1976.

All patients, including those assigned to the surgical group, received medical therapy. Surgically treated patients were advised to modify risk factors and those who developed recurrent or worsening angina during follow-up were usually given nitrates and beta-adrenergic blocking agents.

The present study group is a subset of the 390 patients who were randomized to receive coronary artery bypass graft surgery (Fig. 1). Exercise testing before randomization within a mean time of 6 days from enrollment was performed in 292 patients (75%); the 174 patients (45%) who had exercise tests before and 6 months after surgery form the basis of this report.

Exercise testing. Although a graded treadmill exercise test using the Bruce protocol (16) was a study requirement, its absence did not constitute a reason for exclusion from randomization. The exercise test was analyzed for the presence of ≥1 mm of horizontal or downward ST segment depression measured 0.08 s after the J point of the electrocardiogram (ECG) and for the occurrence of anginal chest pain either during exercise or during recovery. Silent myocardial ischemia in this report was defined as the presence of ischemic ST depression without anginal chest pain during exercise testing.

Cardiac catheterization. Selective coronary angiography and left ventriculography were performed in all patients according to a common protocol. Angiographic requirements for participation in the randomized trial included the presence of clinically important, operable coronary artery disease, which was defined as a ≥70% narrowing of the luminal diameter in the left anterior descending, left circumflex or right coronary artery or their major branches or a 50% to 70% diameter narrowing of the left main coronary artery.

A left ventricular wall motion score (range, 5 to 30) was calculated on the basis of a subjective grading of the left ventricular wall motion from the right anterior oblique projection of the left cineventriculogram, as previously reported (15).

Statistical analyses. Group differences at baseline were assessed by the chi-square test for discrete variables and by the two-sample t test for continuous variables. Survival curves were calculated with the life-table method and displayed all-cause mortality carried out to 12 years of follow-up. The log-rank statistic, computed from all the follow-up data, was used to assess the statistical significance of the observed differences among survival curves of the three patient groups (17).

Results

Surgical results. Operative mortality and perioperative myocardial infarction rate were 1.4% and 6.4%, respectively, for the patients in the CASS randomized trial who were assigned to receive coronary artery bypass graft surgery. Complete revascularization of all stenosed coronary artery vessels was attempted in every patient. The average number of bypass grafts placed was 2.7/patient. Repeat coronary arteriography, performed in a small unselected group of patients within 60 days of operation, revealed a 90% graft patency rate.

Entry characteristics (Table 1). The 216 randomized surgical patients who did not undergo exercise testing preoperatively and at 6 months postoperatively differed only in the number of diseased coronary vessels at baseline from the 174 randomized surgical patients who underwent exercise testing and who formed the study group (Table 1). Although the group undergoing exercise testing had more severe coronary artery disease at baseline, their survival rate at 12 years was...
Table 2. Baseline Characteristics of 174 Patients Based on the Preoperative Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (Silent Ischemia)</th>
<th>Group 2 (Symptomatic Ischemia)</th>
<th>Group 3 (No Ischemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤60 years</td>
<td>85 (42)</td>
<td>86 (90)</td>
<td>92 (32)</td>
</tr>
<tr>
<td>Male Gender</td>
<td>94 (88)</td>
<td>94 (94)</td>
<td>94 (94)</td>
</tr>
<tr>
<td>CHF score (0 to 4)</td>
<td>0 (77)</td>
<td>87 (77)</td>
<td>72 (72)</td>
</tr>
<tr>
<td>CCS angina class</td>
<td>None</td>
<td>7 (7)</td>
<td>50 (50)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>71 (9)</td>
<td>40 (9)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Coronary vessels with ≥70% narrowing</td>
<td>1 (15)</td>
<td>2 (21)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>LV wall motion score ≥10</td>
<td>65 (91)</td>
<td>91 (91)</td>
<td>75 (75)</td>
</tr>
<tr>
<td>LV end-diastolic pressure ≤18</td>
<td>90 (88)</td>
<td>88 (88)</td>
<td>94 (94)</td>
</tr>
<tr>
<td>Final exercise stage ≥2</td>
<td>94 (92)</td>
<td>92 (92)</td>
<td>100 (100)</td>
</tr>
</tbody>
</table>

*p < 0.01 versus group 1. All values represent percent of patients. Abbreviations as in Table 1.

almost identical to that of the group that did not undergo exercise testing (75% vs. 76%, respectively, p = 0.86).

Patient groups (Tables 2 and 3). The 174 study patients were classified into three groups on the basis of the preoperative exercise test results. Group 1 (silent ischemia) consisted of 52 patients with ≤1 mm ischemic ST depression but without angina during the test; group 2 (symptomatic ischemia) comprised 90 patients who had both ischemic ST depression and angina, and group 3 (no ischemia) consisted of 32 patients who had neither ST depression nor angina.

The baseline demographic, clinical, angiographic, and exercise test characteristics among the three groups of patients preoperatively are shown in Table 2. The three groups were similar with respect to age, gender, severity of congestive heart failure, number of diseased coronary vessels, left ventricular score, left ventricular end-diastolic pressure and the final exercise stage achieved. Group 1 patients had less severe angina and a higher prevalence of prior myocardial infarction compared with group 2 patients. Thirty-seven percent of group 1 patients had no history of anginal symptoms compared with 7% of group 2 patients (p < 0.01). Postoperatively, the three groups of patients did not differ in any important baseline characteristic (Table 3).

Prevalence of ischemia at 6 months. Among the 174 study patients, 30% were in group 1 (silent ischemia at baseline and 29% were in this group at 6 months. By contrast, the frequency of patients in group 2 (symptomatic ischemia) decreased from 52% preoperatively to 6% postoperatively (p < 0.001), and the percent of patients in group 3 (no ischemia) increased from 18% preoperatively to 65% postoperatively (p < 0.001). Thus, although the percent of patients with silent ischemia (group 1) during exercise testing did not change postoperatively, the frequency of symptomatic ischemia (group 2) decreased significantly and the percent of patients without ischemia (group 3) increased significantly.

When the 52 patients with silent ischemia during preoperative exercise testing were analyzed separately, the majority (54%) showed no ischemia during the postoperative exercise test but 40% continued to have signs of silent ischemia (Fig. 2). Of patients with symptomatic ischemia preoperatively,
Table 4. Patient Groups at Baseline and at 6 Months and 18 Months Postoperatively

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>6 Months</th>
<th>18 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Group 1</td>
<td>45 33%</td>
<td>43 31%</td>
<td>53 40%</td>
</tr>
<tr>
<td>(silent ischemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>70 51%</td>
<td>8 6%</td>
<td>6 4%</td>
</tr>
<tr>
<td>(symptomatic ischemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>22 16%</td>
<td>86 63%</td>
<td>76 56%</td>
</tr>
<tr>
<td>(no ischemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.01 versus baseline. All data are expressed as number and percent of patients.

64% showed no ischemia at 6 months, whereas 27% had silent ischemia (Fig. 2).

Results of exercise testing at 18 months (Table 4). One hundred thirty-seven patients underwent exercise testing before and at 6 and 18 months after coronary bypass surgery. By 18 months, 40% of the study group had evidence of silent ischemia and 4% and 56%, respectively, had symptomatic ischemia or no ischemia (both p < 0.01 compared with preoperative exercise test groups).

Long-term survival. The 12-year cumulative survival rate based on the 6-month exercise test groups was significantly higher for patients in group 3 (80%) than for patients in group 1 (68%) or group 2 (45%) (Fig. 3). Repeat coronary artery bypass graft surgery during the follow-up period was performed in 10% of group 1 patients, 21% of group 2 patients, and 9% of group 3 patients (p = NS). Percutaneous transluminal coronary angioplasty was performed in 6% of group 1, 4% of group 2, and 6% of group 3 patients (p = NS).

Discussion

Survival after coronary bypass surgery. The prognosis of patients after coronary artery bypass graft surgery depends on many factors, most prominently left ventricular function and graft patency (18-20). In a previous study (21) using data from the CASS registry, we found that the final exercise stage achieved during exercise testing before operation and the preoperative left ventricular wall motion score were independent predictors of survival after coronary bypass surgery. Postoperative exercise testing was not performed in that study. Because many procedures, including angioplasty of occluded grafts (22,23), are being performed to treat patients with postoperative ischemia, it is important to determine whether the precipitation of ischemia during provocative testing postoperatively has prognostic significance.

Prevalence of postoperative ischemia. Of the 36% of patients who had ischemia during a 6-month exercise test postoperatively, 82% (51 of 62) did not have associated angina. At 18 months postoperatively, there was a 44% prevalence of ischemia, which was silent in 90% (55 of 61). The 36% prevalence of postoperative ischemia at 6 months in our study is similar to the 28% prevalence rate found by Dubach et al. (22), who performed exercise testing in 296 patients. Using the ambulatory ECG monitor to assess postoperative ischemia, Kennedy et al. (7) found a frequency of 27% at 12 months. Among the 50 patients manifesting ischemia, only 1 patient had associated angina. Eegstrup (5) determined that 33% of 36 patients who underwent coronary bypass graft surgery for chronic stable angina showed ischemia during ambulatory ECG monitoring at 3 months postoperatively. All the episodes of ischemia were silent.

One postulated reason (24) for the development of silent rather than symptomatic ischemia in some patients is that silent ischemia occurs in patients who have a lesser amount of ischemic myocardium. Our results showed that 27% of the 90 patients who demonstrated symptomatic ischemia during preoperative exercise testing had silent ischemia during exercise testing 6 months after coronary bypass surgery. It is possible that these patients had incomplete revascularization despite a lesser amount of ischemic myocardium postoperatively, although we do not have extensive postoperative catheterization data to support this hypothesis.

Figure 3. Cumulative survival rates for patients in groups 1, 2, and 3. The numbers in parentheses refer to the number of patients who were alive and followed for a particular time period. The 12-year survival rate was significantly better for group 3 compared with group 1 or 2. ST↓ = ST depression.
Prognosis of postoperative ischemia. Previous studies (25-27) on the usefulness of postoperative exercise testing to predict coronary graft status have shown a poor correlation between the ST segment changes and graft patency. One recent study (6) found that ischemic ST depression during postoperative exercise testing was not associated with a higher risk of death or infarction. The metabolic equivalent (MET) level achieved on the treadmill exercise protocol was the only exercise variable predictive of adverse prognosis. That study (6) was limited by the long time frame that the exercise test was performed after coronary bypass surgery (mean, 4.2 ± 3.8 years) and the short period of follow-up (2 years).

The present study incorporated a prospective design in which patients were exercised 6 months after surgery and then followed for > 12 years. Our results documented that both silent and symptomatic ischemia during exercise testing 6 months postoperatively had an adverse effect on long-term survival. These results support a recommendation that postoperative ischemia with or without associated angina should be treated vigorously with anti-ischemic medications and, if these are unsuccessful, possibly with revascularization to try to improve the prognosis. However, prospective, randomized studies are needed to determine whether treatment of postoperative ischemia does alter prognosis.

A previous study (28) of CASS patients with silent myocardial ischemia during exercise testing indicated that the survival in subsets of patients with severe coronary artery disease and abnormal left ventricular function appeared to be enhanced by coronary artery bypass graft surgery. However, that report analyzed patients who were enrolled in the CASS registry study and who had preoperative silent ischemia, whereas the present study evaluated the prognostic significance of postoperative ischemia among patients enrolled in the CASS randomized study.

Earlier studies (4,5,7) using the ambulatory ECG monitor to evaluate postoperative ischemia have yielded conflicting results. Crea et al. (4) found that, after coronary bypass surgery, the results of the ambulatory ECG monitor did not improve the sensitivity of exercise testing in identifying patients with angiographically incomplete myocardial revascularization. Kennedy et al. (7) reported that ambulatory ECG-detected silent ischemia during the 1st year after bypass surgery was not associated with an adverse prognosis. In contrast, Egstrup (5), utilizing the ambulatory ECG monitor 3 months after bypass surgery in 36 patients with chronic stable angina, found that asymptomatic myocardial ischemia was correlated with a significant cumulative probability of cardiac events. Multivariate analysis of 11 variables showed that silent ischemia was the most powerful predictor of cardiac events.

Limitations. Although exercise testing was part of the CASS protocol, it was not performed in 25% of the randomized surgical cohort preoperatively or in 55% of the cohort at 6 months postoperatively. Comparison of patients who did or did not undergo exercise testing failed to reveal substantial survival differences.

Because repeat cardiac catheterization was not performed in the majority of patients at 6 months postoperatively, we cannot determine the mechanisms responsible for the development of postoperative ischemia.

Current surgical revascularization techniques are different from the procedures used during the CASS randomization period. Greater use of internal mammary arteries as conduit vessels (29) and the widespread utilization of platelet-inhibitor medications (30) after coronary bypass surgery during the past few years would probably reduce the prevalence of postoperative ischemia compared with our results from > 10 years ago.

Clinical implications. The presence of provocative ischemia, whether documented by exercise testing or by ambulatory ECG monitoring, is associated with an adverse prognosis among patients with stable or unstable angina pectoris or after a myocardial infarction. Our results extend these findings to the postoperative patient and suggest that postoperative ischemia, when documented by exercise testing, is also associated with higher risk and is present in a substantial percent of postoperative patients. Whether this additional risk can be lowered by medications or by revascularization procedures is uncertain and should be evaluated by prospective, randomized trials.

References


