Coronary Surgery After Recurrent Myocardial Infarction: Progress of a Trial Comparing Surgical with Nonsurgical Management for Asymptomatic Patients with Advanced Coronary Disease

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SUMMARY A randomized trial of surgical vs nonsurgical management was carried out in men 60 years of age or younger who had recovered from a recurrent myocardial infarction. Of 205 patients considered, 100 had few or no symptoms and had coronary vessels favorable for bypass grafting; these patients fulfilled the trial conditions and were randomized (50 surgical and 50 nonsurgical). In 41 patients (elective nonsurgical group). randomization was not considered justifiable because of relatively unfavorable coronary anatomy or severe left ventricular dysfunction. Nineteen patients had elective surgery because of disabling angina despite full medical treatment or because of significant left main coronary stenosis. In 45 patients, coronary angiography was not undertaken because of medical contraindications or reluctance of the patient to enter the study.

Actuarial survival curves (mean follow-up 4.5 years) show an annual mortality rate of 3-4% per year for all investigated patients, and no advantage for the randomized surgical over the randomized nonsurgical group. The results suggest that in the absence of disabling angina or left main coronary artery stenosis, coronary artery surgery need not be advised for survivors of recurrent infarctions who have severe coronary artery disease. Moreover, the prognosis for the group of patients not treated surgically appears to be better than has been previously described.

AORTOCORONARY BYPASS GRAFTING for coronary artery disease has become a common form of treatment. According to one estimate, more than 60,000 such operations were carried out in the United States in 1976 and possibly 80,000-100,000 in 1977.1 Up to March 1978, 1248 patients were reported who had been randomized for surgical or nonsurgical treatment after preliminary coronary angiography. Six of these trials, which involved patients with stable or unstable or angiographic pectoris, failed to show a reduction in subsequent mortality or infarction after bypass grafting. In only one report of 113 patients with left main coronary stenosis did the mortality rate appear to be reduced by operation. Although two more recent reports8, 10 suggested that symptomatic patients with severe coronary artery disease have a real, though small, improvement in survival after surgery, Braunwald reported a "growing uneasiness that by simple common consent rather than by rational analysis of data we may be opting for general use a form of treatment that has yet to prove itself."11

One group of patients for whom therapeutic decisions are particularly difficult are those who have severe coronary artery disease, yet have few or no symptoms. For these patients, the physician cannot guarantee an improved quality of life after operation, so that the benefits to be expected are prolongation of life or prevention of further myocardial infarction. Many such patients have survived a second or third myocardial infarction. In a previous study12, 13 we found the late mortality rate of hospital patients who had survived recurrent myocardial infarction to be 50% at 3 years and 64% at 6 years. These patients had not been studied by angiography, but their mortality rate was comparable to that of patients reported at about that time whose angiograms showed three-vessel coronary disease and a damaged left ventricle.14, 15

The present report describes a study of prognosis of men ages 32-60 years who had survived a documented recurrent infarct. Patients who had few symptoms with severe coronary disease and favorable vessels for grafting shown by coronary arteriography were randomized for nonsurgical treatment or aortocoronary vein graft surgery. Preliminary results from the study have been published.16, 17

Patients and Methods

Patients were men, ages 32-60 years, who had survived two or three myocardial infarcts, with the infarcts at least 1 month apart. The diagnosis of infarction in each instance was based on at least two of the following criteria: (1) characteristic clinical presenta-
tion; (2) pathologic Q waves and/or ST- and T-wave abnormalities in the ECG, with evolutionary changes; and (3) a rise in aspartate aminotransferase (Asp At) activity to 50 IU/l or greater.

Patients were enrolled in the trial between January 1972 and February 1979. Sixty-six percent had been treated in the coronary care unit at Green Lane Hospital, and all patients with two or more documented infarctions were considered. The other 34% had been referred from other hospitals in the Auckland region. Patients entered the study at the time of discharge from hospital, when they were advised that a trial of medical or surgical treatment would be recommended after investigation by coronary arteriography. They were informed that surgery would be advised for some cases, but because the role of surgery was not yet firmly established for all patients, it was not recommended for everyone. If nonsurgical management were advised, surgery could always be considered later if the situation changed or their condition demanded it. This approach and subsequent randomization were approved by a representative group of physicians in Auckland and by the Ethics Committee of the New Zealand Medical Research Council.

Patients were readmitted to hospital 2 months after infarction. Graded exercise testing was performed, as were left ventriculography and coronary cineangiography using either the Judkins or the Sones technique. Patients were kept in hospital for 24 hours after the angiograms, during which time fasting serum lipids and glucose tolerance were measured.

For analysis of the cineangiograms, ejection fraction was measured from a single-plane angiocardio gram in the right anterior oblique position using our modification (Bass NM, Whitlock RML, Vedder M, Partridge JB, Wattie WJ, Brandt PWT: manuscript in preparation) of an area-length method. For the coronary angiograms, a myocardial score was used; this expresses the severity of left ventricular arterial obstructive disease by considering not only the degree of stenosis of any number of arterial branches, but also their importance in terms of the amount of myocardium supplied. In this respect it reflects more accurately the severity of disease than do the terms one-, two- and three-vessel disease, or the arterial score of Friesinger, Page and Ross.

The clinical features and angiograms were then discussed at the weekly hospital cardi osurgical conference and a firm decision was made whether the patient was to be randomized or whether elective surgical or nonsurgical treatment was recommended. Elective surgery was advised for two specific indications: left main coronary stenosis of 75% or more of cross-sectional area or angina (in addition to two infarcts) that was considered to be disabling despite adequate medical treatment. The clinical decision that angina was severe enough to warrant surgery had been made before cineangiography was undertaken, and was based on the history and the result of the exercise test. Elective nonsurgical management was recommended if the angiographic assessment of atheromatous involvement of the distal vessels revealed that surgery would be of doubtful value, particularly when unfavorable vessels were associated with poor left ventricular function, if insufficient viable myocardium seemed to be compromised to make grafting worthwhile, or if minimal or no coronary stenoses were present. All other patients were then randomized by the envelope method to either surgical or nonsurgical treatment. Surgical patients were placed on the surgical waiting list, which resulted in a mean delay before operation of 5 months (range 1–10 months). Standard surgical techniques were used and complete revascularization was the goal for all patients. The mean number of distal graft anastomoses was 2.8 per patient (range 1–5).

All patients have been seen twice a year for follow up, when their anginal status, occurrence of more infarctions, drug treatment, smoking habits and cardiovascular signs have been noted. Survival has been assessed by the actuarial method, with a median follow-up of 4.5 years (range 1–8 years).

Results

The mean age of the patients was 51 years (range 32–60 years) at the time of entry to the trial. One hundred ninety of the patients had had two infarctions and 15 had three infarctions. The interval between the first and the most recent infarct was 3.5 years (range 1 month to 16 years). Figure 1 shows the status of the trial when enrollment stopped in February 1979. Of 205 patients considered for investigation, 45 were in the group not investigated because of cardiac failure continuing after the acute stage of infarction, another medical condition which it was judged might shorten life, sudden death between discharge from hospital and planned admission for the investigation, or patient...
refusal to enter the study. Reasons for exclusion are detailed in table 1.

Of the remaining 160 patients, 19 (12%) had either left main coronary stenosis (two patients) or disabling angina (17 patients), and so were recommended for elective coronary surgery. In 41 patients (the elective nonsurgical group, comprising 25% of those investigated) surgery was considered to be contraindicated for the purpose of the trial because of unfavorable distal vessels, often with poor left ventricular function (38 patients), or minimal or no coronary disease (three patients). The proportion of patients not considered for surgery was a result of the stricter-than-usual criteria for operability that we adopted for these relatively asymptomatic patients. The remaining 100 patients (63%) were randomized for surgical or nonsurgical treatment (50 surgical and 50 nonsurgical).

We considered the possibility that referral of 34% of patients from other hospitals might have introduced a bias in favor of one of these groups. Of randomized surgical cases, 44% had been referred, of randomized nonsurgical cases 36%, of elective nonsurgical 27%, of elective surgical 42% and of noninvestigated patients 24%. All suitable patients from our own hospital had been considered for the study, so we concluded that referral of patients from other hospitals had not materially biased the selection of cases.

The severity of coronary artery disease and impairment of left ventricular function at the time of angiography are shown in figures 2 and 3. A myocardial score greater than 5 corresponds in severity to two-vessel disease and greater than 10 to three-vessel disease. All but three patients (who were in the elective nonsurgical group) had a score greater than 5 and approximately two-thirds had a score greater than 10. Figure 3 shows that two-thirds of patients had impairment of left ventricular function, evidenced by an ejection fraction of less than 50%. Although there appears to be a trend toward lower ejection fraction for randomized surgical than for randomized nonsurgical patients (fig. 3), this is not statistically significant.

Nine patients in the randomized nonsurgical group and three in the elective nonsurgical group were changed to the elective surgical group at 7 months to 5½ years (mean 2 years) after the initial decision on treatment was made. This was done because the development of disabling angina, not present at the time of investigation, was judged to necessitate surgery for control of symptoms. Currently, we are planning transfer of two more patients from the randomized nonsurgical group. These patients were restudied angiographically before surgery was undertaken, and in no case was there any important change from the first investigation either in the severity of coronary artery disease or in left ventricular ejection fraction.

At a mean follow-up time of 4.5 years, 62 (30%) of the 205 patients died. Thirty-three of these deaths were among the 45 patients who were not investigated. Of patients investigated, six deaths were in randomized surgical patients, five in the randomized nonsurgical group, 12 in the elective nonsurgical, and six in the elective surgical groups. Four of the elective sur-
surgical deaths were in patients who had crossed over from the randomized or elective nonsurgical groups. All but one of the deaths in investigated patients were cardiac, usually sudden death without premonitory symptoms. The noncardiac death was from cancer in a randomized surgical patient during the third year of follow-up. Of the remaining deaths in surgical patients, two were at the time of operation, two occurred while the patients were in hospital after the operation, and one was in a patient awaiting surgery. Of the four postoperative deaths, two were in patients who had crossed over, because of disabling angina, from the randomized nonsurgical to the elective surgical group.

Actuarial survival curves for the various groups of patients are shown in figures 4–7, and a detailed analysis of deaths, crossovers and further nonfatal infarction in randomized patients is shown in table 2. For the whole group of patients (fig. 4), there was a 15% mortality rate in the first year, mostly because of patients who died before investigation or in whom investigation was considered unjustified because of cardiac failure or concurrent life-threatening disease (table 1). In the next 5 years of actuarial follow-up, however, the mortality rate fell to 3–4% per year.

There was no difference in survival between randomized surgical and randomized nonsurgical patients. The mortality rate was higher, however, among the elective nonsurgical patients (fig. 5), who had lower ejection fractions than the randomized cases (p < 0.01, fig. 3). For the purpose of actuarial analysis, patients who crossed over from the two nonsurgical groups to the elective surgical group were included in the nonsurgical group until the time of crossover, and their subsequent survival was analyzed in the elective group from the time they were operated upon. Thus, the elective surgical group contains the 19 patients who were originally included, as well as the 12 patients who crossed over.

Twenty-seven further nonfatal infarctions occurred among the 160 investigated patients. Two occurred at the time of operation in the surgical patients, and the frequency of recurrent nonfatal infarction was similar in the randomized nonsurgical and surgical groups.
(table 2). Because disabling angina was treated surgically by election either at the time of initial study or subsequently in the nonsurgical groups, this symptom was seen only in surgically treated patients, three of whom have disabling chest pain for which further operation is not thought to be justified because of unsuitable coronary anatomy. Of the remaining patients, most enjoy good health, and almost all who have not reached retiring age are working.

The 91 investigated patients who were not operated upon (50 randomized nonsurgical and 41 elective nonsurgical) were next examined to see whether prognosis could have been predicted by the angiographic findings. Within this group, a high myocardial score of greater than 10 did not predict a higher subsequent mortality than did a score of lower than 10 (fig. 6). However, poor left ventricular function, evidenced by a low ejection fraction, was predictive of a higher mortality, as all 17 deaths in nonsurgical patients occurred in those with an ejection fraction of less than 50% (p < 0.01; fig. 7).

Figure 8 contrasts the mortality rate of the present group of nonsurgical patients with that of two comparable published series. Four curves are depicted: patients from the present series who were investigated, treated without operation, and had a myocardial score greater than 10; all patients from the present series, however treated, and whether they were investigated or not; a frequently quoted series of patients with three-vessel disease described from the Cleveland Clinic; and survivors of a recurrent myocardial infarct who were originally reported from Auckland but were not studied by arteriography. Survival of the present investigated patients who did not have an operation was considerably better than for these previously reported series, and the difference persists when we included patients in the present series in whom investigation was considered inadvisable.

The smoking habits and drug treatment of the investigated patients are shown in tables 3 and 4. As a result of counseling, most smokers either stopped or...
modified their smoking habits. Most patients received no medication, but β-blocking drugs were used if angina occurred more than occasionally and digoxin and diuretics were used for control of cardiac failure.

Further coronary arteriography at 7 months to 5 years (mean 2 years, 9 months) was done in 33 of the 50 randomized surgical patients. The proportion of patent grafts is shown in table 5. All but five of the 33 patients had at least one patent graft at follow-up.

Table 3. Smoking History of Recurrent Infarct Patients

<table>
<thead>
<tr>
<th>Cigarettes smoked daily</th>
<th>Before entry to the trial*</th>
<th>After entry to the trial*</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or stopped</td>
<td>65 (42%)</td>
<td>118 (77%)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>10 (6%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>10-19</td>
<td>24 (15%)</td>
<td>14 (9%)</td>
</tr>
<tr>
<td>20-29</td>
<td>34 (22%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>30</td>
<td>24 (15%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

*Data available for 152 patients.

Table 4. Drug Treatment of Recurrent Infarct Patients

<table>
<thead>
<tr>
<th></th>
<th>Randomized surgical (n = 50)</th>
<th>Randomized nonsurgical (n = 50)</th>
<th>Elective surgical (n = 19)</th>
<th>Elective nonsurgical (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Diuretic</td>
<td>5</td>
<td>12</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>β blocker</td>
<td>6</td>
<td>11</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 5. Graft Patency in 33 Patients at Mean Follow-up of 3 Years

<table>
<thead>
<tr>
<th>Grafts applied*</th>
<th>No. of pts</th>
<th>No. of grafts patent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>10</td>
<td>2 in 6 pts; 1 in 3 pts; 0 in 1 pt.</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>3 in 7 pts; 2 in 6 pts; 1 in 2 pts; 0 in 3 pts.</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4 in 2 pts; 2 in 2 pts.</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0 in 1 pt.</td>
</tr>
</tbody>
</table>

*Number of distal anastomoses. Total patency rate: 62 of 95 (65%).

Discussion

The present study supplements previous reports\(^2\)\(^-\)\(^10\) of randomized trials of surgical treatment with regard to the incidence of subsequent myocardial infarction and death in patients with ischemic heart disease. However, our study is unique in that angina pectoris was not the major presenting symptom of patients admitted to the trial. In studying patients with recurrent myocardial infarction, our aim was to define a group with a poor life expectancy but who nevertheless did not have severe continuing symptoms. We accepted that surgical treatment has a proved place for the relief of angina that cannot otherwise be controlled and that patients should not be denied operation if their angina is severe despite full medical treatment.

Inherent in this philosophy is acceptance that some patients would need elective surgery for control of symptoms and that others would have to cross over from the nonsurgical to the surgical group if they developed severe angina after the initial evaluation. Moreover, we accepted the evidence\(^8\) that surgical treatment prolongs life in patients with significant left main coronary stenosis, so all such patients should be operated upon electively. Although this inevitably causes difficulties in analysis of the data, the problem has been dealt with by considering a separate elective surgical group for actuarial analysis and including crossover patients in this group from the time of operation.

The striking finding in the study is not so much the lack of any apparent difference in mortality between surgical and nonsurgical patients, as the unexpectedly low mortality rate in the investigated patients regardless of treatment. This mortality rate of 3–4% per year contrasts with the annual mortality rate of
10–15% for patients with disease of equivalent severity12–15, 22, 23 (fig. 8). One reason for this difference may be our selection of relatively young low-risk patients for investigation. Patients with overt cardiac failure were not investigated in our study, and 11 of 12 patients who were not investigated because of failure persisting after the infarct died. 

In our earlier study,12–15 men and women of all age groups were included, but the present series is confined to men under 60 years of age. Again, our policy of delaying investigation until 2 months after the recurrent infarct meant that nine deaths occurred between discharge from hospital and the date planned for angiography. However, the difference in mortality rate persists when the patients who were not investigated are included (fig. 8), and if the first-year deaths are disregarded, inclusion of the “not-investigated” group does not alter the subsequent actuarial curve very much. Earlier series may not, however, be strictly comparable. Patients who were studied during the early years of coronary arteriography and coronary surgery14, 15, 22, 23 may have been a highly selected group with an unusually bad prognosis. Patients in the present study may have had an unusually favorable prognosis for ventricular damage with two- or three-vessel disease.

The low mortality rate in the present study does agree, however, with that found in the Veterans Administration trial reported in 197724 and it supports the trend toward a lower mortality rate from ischemic heart disease during the last 10 years.28 Studies showing a high mortality rate for three-vessel disease or recurrent myocardial infarction were done during the 1960s, and our patients were studied during the 1970s. The unexpectedly low mortality rate in this trial was not due to β-blockade; most of the patients were not taking β-adrenoceptor blocking drugs (table 4). It may have been related to careful supervision and reassessment of symptoms, with surgery offered when severe symptoms developed. Most of the patients stopped smoking and were asked about it specifically at each of the 6-month follow-up visits; this may have had some significance. Attempts to define a higher-risk group suggested that significant left ventricular damage (ejection fraction < 50%) was a more serious prognostic factor than severe coronary artery disease (myocardial score > 10). This supports our previous findings of the serious long-term implications of cardiac failure at the time of infarction.12, 13 Perhaps after two myocardial infarctions, these patients had a well-developed collateral circulation (not included in the myocardial score), so severe arterial obstructions were less important for prognosis. The degree of collateral development may have to be included in the myocardial score before it contributes to a prognostic assessment.

A disadvantage of a clinical trial of this nature carried out at a single institution on a carefully defined group of patients is that the rate of recruitment is slow and fewer cases are studied than in many multicenter trials. This disadvantage must be weighed against the advantages: Clinical judgments have been made by the same people, the procedure for randomization has been uniform and unbiased, and surgery has been performed uniformly. Adequate revascularization has been achieved, with a mean number of 2.8 grafts per patient. Although the 5–6-year actuarial mortality figures (figs. 4–7) must be accepted with reservation because of the small numbers, the mean follow-up time of 4.5 years allows for reasonable confidence in the 2–4-year survival figures.

Our results do not give strong support for the use of surgery in relatively asymptomatic patients with three-vessel disease who have survived more than one infarction. Four cases, however, emphasize the difficulty in interpreting the results of a randomized trial of surgical treatment. One of the surgical patients in the present trial died of a noncardiac cause (carcinoma) and another died 1 month after randomization while waiting for operation. Two of the nonfatal reinfarctions in the surgical patients occurred within 2 months after randomization, while the patients were awaiting operation. The crossover patients are also difficult to classify. Three of these patients who started in the randomized nonsurgical group have died, two at the time of operation. Nevertheless, reclassification of these cases would not affect our conclusion that the generally satisfactory results of nonsurgical management for patients after recurrent myocardial infarction do not justify the use of surgery in the absence of disabling symptoms. If severe angina does develop, surgery gives good symptomatic relief and may possibly prolong life. We think it unlikely that recruitment of further cases would alter these conclusions, so we have closed entry to the trial, but will continue actuarial follow-up of patients already studied. The apparently improving outlook for patients with chronic ischemic heart disease treated without operation further emphasizes that large groups of treated and control patients must be followed for a long period.

Acknowledgment

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