Research Related to Surgical Treatment of Coronary Artery Disease

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EUGENE H. BLACKSTONE, M.D., AND ALBERT OBERMAN, M.D.

SUMMARY In the past 20 years, basic and clinical research have provided new information on coronary artery surgery. For example, several studies have shown that coronary artery bypass grafting is more effective than medical treatment in relieving the symptoms of chronic disabling angina pectoris. However, we still do not have definitive answers to many questions. What factors in the patient, in the operation and in the care after operation determine success in surgical treatment? Does the operation prolong useful life? Is the operation affordable? These questions are difficult. Further research is needed to solve complex problems relating to surgical vs medical treatment of coronary artery disease.

THE BASIC and clinical research of the last 20 years has provided important new information about coronary artery surgery. Yet, important problems remain. Among the questions that must be answered are: What factors in the patient, in the operation and in postoperative care determine the outcome of surgical treatment? Does the operation prolong useful life? Is the operation affordable?

Knowledge About Coronary Artery Surgery

Before examining these questions, we shall briefly review some of our knowledge about the surgical treatment of coronary artery disease.

Hospital Mortality

The risk of coronary bypass surgery is low when it is performed under the proper circumstances. This is obviously important, for if hospital mortality for uncomplicated cases is relatively high — for example, 5% — the late results are affected unfavorably.

In discussing hospital mortality from the operation, we must have current information, because continuing improvements in intraoperative techniques have lowered the risks of the operation. For example, we may look at our experience at the University of Alabama Medical Center in 1977. In that year, we performed primary isolated coronary artery bypass grafting in 757 patients. Many of these patients had significant left ventricular dysfunction and very low ejection fractions, since in general only left ventricular dysfunction so severe as to result in the syndrome of right-heart failure is a contraindication in operation. Seven patients died in hospital, for an overall mortality of 0.9% (table 1).

In our 1977 experience, the risk of the operation was related to age (table 2). Hospital mortality was 20% for patients older than 70 years, compared with 0.4% for those younger than 70 years. (p for difference < 0.0001). Most of the patients were 50–70 years old at operation, and in this group of 551 patients, one died, for a hospital mortality of 0.2% (70% CL* 0.02–0.6%). Parametric analysis confirms the highly significant relation between age and risk of operation in this experience (p < 0.0005) (fig. 1). We believe this information has important implications concerning the place of this operation in the management of coronary artery disease in persons older than 70 years.

These data include all types of patients. This must be ascertained in any surgical report. The Veterans Administration Cooperative Study, for example, includes only patients with chronic stable angina pectoris.

Complete revascularization (grafting to all stenosed or obstructed coronary arterial trunks and branches 1 mm or more in internal diameter) is usually possible and can be accomplished without increasing the hospital mortality. The trends from 1970–1976 in 2405 patients at our institution (fig. 2) show that the number of grafts (or distal anastomoses) has increased while hospital mortality has decreased. In 1977 the average number of distal anastomosis per patient was 3.4, and the hospital mortality 0.9%. In 1977, only 5% of the patients had just one distal anastomosis. In contrast, 47% of the patients had four or more distal anastomoses (table 1). Yet there is no significant difference in the hospital mortality (p = 0.45) between those in whom one or two distal anastomoses were done and those in whom four or more were done. A chi-square test for trend of hospital deaths with increasing number of anastomoses done on table 1 also shows no significant relation between the number of distal anastomoses and hospital mortality (p = 0.54).

Sequential grafting — making several distal anastomoses to one vein — is necessary for complete revascularization. The technique has had good results. Work at the Montreal Heart Institute has shown that sequential anastomoses to small vessels do stay open in many cases when an appropriate technique is used.

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*CL refers to the 70% confidence limits around the point estimate throughout this paper.
Complete revascularization has been stimulated by data published by several centers, including the Cleveland Clinic and the Mayo Clinic, that indicate that the completeness of revascularization is directly correlated with the probability of the patient's being asymptomatic after the operation.

**Graft Patency**

At least 80% of grafts and anastomoses stay open and are functional in the first 3–5 years after operation. Patency rates have been steadily increasing with improved surgical techniques. Of course, because the operation is relatively new, no information on graft patency beyond about 8 years postoperatively is available.

**Relief of Angina Pectoris**

Several studies have demonstrated that coronary artery bypass grafting is very effective in relieving the symptoms of chronic disabling angina pectoris — significantly more effective than medical treatment. Data from a small but carefully performed prospective study by Mathur and colleagues from the Veterans Administration Hospital in Houston are illustrative (table 3). One year after surgery, 75% of surviving surgically treated patients were completely free of symptoms, compared with 13% of surviving patients treated medically. Mathur and colleagues and others have also shown by objective testing that exercise tolerance is significantly improved by operation but not by medical treatment.

### Table 1. Primary Coronary Artery Bypass Grafting,* University of Alabama, Birmingham

<table>
<thead>
<tr>
<th>No. of distal anastomoses</th>
<th>% of patients</th>
<th>No. pts</th>
<th>Hospital deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>1</td>
<td>5%</td>
<td>36</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.8%†</td>
</tr>
<tr>
<td>2</td>
<td>122</td>
<td>1</td>
<td>0.8%</td>
</tr>
<tr>
<td>3</td>
<td>245</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td>4</td>
<td>214</td>
<td>2</td>
<td>0.9%</td>
</tr>
<tr>
<td>5</td>
<td>113</td>
<td>3</td>
<td>2.7%</td>
</tr>
<tr>
<td></td>
<td>47%</td>
<td></td>
<td>1.4%†</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>—</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>—</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>757</strong></td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

CL = 70% confidence limits.

*Exclusive of those with concomitant valve surgery, left ventricular resection, or extracardiac vascular surgery.

†p for difference < 0.0001.

### Table 2. Primary Coronary Artery Bypass Grafting,* University of Alabama, Birmingham, 1977

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>No. pts</th>
<th>Hospital deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>20 &lt; 30</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>30 &lt; 40</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>40 &lt; 50</td>
<td>157</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 &lt; 60</td>
<td>361</td>
<td>1</td>
</tr>
<tr>
<td>60 &lt; 70</td>
<td>190</td>
<td>0</td>
</tr>
<tr>
<td>70 &lt; 80</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>757</strong></td>
<td>7</td>
</tr>
</tbody>
</table>

CL = 70% confidence limits.

*Exclusive of those with concomitant valve surgery, left ventricular resection, or extracardiac vascular surgery.
patients who still have symptoms after operation had either incomplete revascularization or graft closure, or progression of disease distal to the anastomosis.\textsuperscript{2, 8, 17}

Questions That Remain

Does Coronary Artery Bypass Grafting Significantly Prolong Useful Life

Beyond the Time That Medical Treatment Can Do So?

This question is very important, but a definitive answer is not available for several reasons. In part, these relate to an earlier question, that of factors relating to surgical success. Patients with coronary disease differ in age, race and sex, and these variations probably affect the natural history of coronary artery disease and the results of medical and surgical treatment. The number of stenosed branches of the coronary arterial tree, and perhaps their location, may be of major importance in determining the results of operations and the natural history of the disease. However, even here our knowledge is fairly crude. For example, a patient with a truly isolated 60% stenosis of the midportion of the anterior descending artery may have a very different natural history from one with a 90% stenosis of the proximal portion of this artery that also involves the origin of a large first diagonal artery and with a stenosis also at the origin of the second diagonal artery. Yet both patients would probably be categorized as having single-vessel disease. The number of distal anastomoses a surgeon might make for the latter of these two patients varies from one to three, so one begins to see the heterogeneity of a surgically treated group of patients with single-vessel disease of the left anterior descending coronary artery. In patients with three-vessel coronary artery disease, the variability in extent of disease and completeness of revascularization are very great. Obviously, the complexities of precisely comparing surgical vs medical treatment are also very great.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Probability of hospital death as a function of age at operation among 757 patients who underwent isolated coronary artery bypass grafting in 1977 at the University of Alabama Medical Center. The solid line represents the point estimates and the dotted lines the 70% confidence limits. Logistic equation for the relationship:

\[
Pr = \frac{1}{1 + \exp[6.6 + 0.83 \times \text{age} + 4.1 \times \text{age}/100]}
\]

where \(Pr = \text{probability of death, } \exp = e, \text{ the base of the natural logarithms and age is in years. Significance level of coefficients: } p(\text{intercept}) < 0.0001; \ p(\text{age}) = 0.0005; \ r = -0.8841.\]

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Early mortality (30-day mortality) and average number of grafts per patient in coronary artery bypass grafting in 2405 patients operated on at the University of Alabama Medical Center. Note that the early mortality decreases with time, while the average number of grafts per patient increases with time. In 1977, seven (0.9%) of 757 patients died in hospital, and an average of 3.4 distal anastomoses were made per patient.

**Table 3.** Symptomatic Status in Coronary Artery Disease Randomized Study\textsuperscript{*}

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Status &gt; 1 year after treatment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>Improved</td>
<td>Same or worse</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>CABG (n = 32†)</td>
<td>24</td>
<td>75%</td>
<td>7</td>
</tr>
<tr>
<td>Medical treatment (n = 30†)</td>
<td>4</td>
<td>13%</td>
<td>19</td>
</tr>
</tbody>
</table>

\(p\) for difference

*Based upon the study by Mathur et al.\textsuperscript{14}

†Surviving patients.

Abbreviation: CABG = coronary artery bypass grafting.
The degree of left ventricular damage already imposed by the coronary atherosclerosis has been shown to affect profoundly the natural history of persons with coronary artery disease, independent of the number of coronary arterial branches with significant stenotic lesions.\textsuperscript{18-20} Therefore, the long-term results of both medical and surgical treatment must be presented in subsets with varying degrees of left ventricular damage, as well as with the other variables we have already mentioned.

Hypertension, obesity and smoking, and other major stigmata of atherosclerosis such as cerebral vascular disease, must also affect the results of any form of treatment, and an ideal analysis of surgical and medical results would require accounting for these. Therefore we must develop mathematical and statistical methods for multivariate analyses of survival distributions so that incremental risk factors can be identified, their relative importance quantitated and predictive equations generated for clinical use.

As already implied, the heterogeneity of surgical techniques certainly requires careful scrutiny in studying the long-term results of surgical vs medical treatment of coronary artery disease. In almost all studies reported to date, including the randomized study of the Veterans Administration (VA)\textsuperscript{4} this factor is largely overlooked, but is very real. The hospital mortality in the VA study for patients with chronic stable angina pectoris from 1972–1974 is 5% — 10 times that of our own (0.4%) for 1977 in patients in the same age group but with all symptoms, not just chronic stable angina. The heterogeneity of practices leading to this important difference must also affect other matters, such as the completeness of revascularization and late graft patency.

Another important variable is the method of protecting the myocardium during the period of cardiac ischemia that is an inherent part of most operations for coronary artery bypass grafting. Intensive research has refined greatly our knowledge of these matters, with an important impact on the results of coronary artery bypass grafting. Myocardial preservation is directly related to the incidence and extent of perioperative myocardial infarction, which in turn has an important effect on both the hospital mortality and long-term results of operation.

Most studies of the efficacy of surgical vs medical treatment for coronary artery disease in prolonging useful life have compared surgical treatment with nonsurgical treatment. Often, the implication has been that the latter is really the natural history of the disease, which seems unlikely. The VA Cooperative Study has raised the question whether the results of medical treatment are changing and are better today than 5–10 years ago, the period that is the source of much of the so-called control data against which surgical treatment is tested. Whether or not this is true, it emphasizes the potential unreliability of this method of evaluation in providing valuable information.

Greene and colleagues\textsuperscript{21} and others have suggested and used a method for evaluating the effect on survival of coronary artery bypass grafting. They compare the survival of patients undergoing this operation with the survival of the population as a whole taken from life tables. This avoids using as the control medically treated patients, who constitute a subset of persons that is itself subject to change in long-term survival because of changing methods and intensity of medical treatment.

We have evaluated some of our own data in this way. For each subset of patients, an age/sex/race-matched life table was constructed from data from the 1974 U.S. Life Tables from the Department of Health, Education, and Welfare.\textsuperscript{22} The survival of the subset was compared with its matched life table, which is of course a stable reference point. Such an analysis indicates that once the patient with single-vessel disease becomes a hospital survivor, his life expectancy is the same as that of the age/sex/race matched general population (fig. 3). Patients with two-vessel disease have a shorter life expectancy to 5 years than the matched general population, but the difference is not great (fig. 4). The 5-year life expectancy of patients who undergo surgery for three-vessel disease is less favorable than that of the matched general population, but by only about 6% at 5 years (fig. 5). The late results in surgically treated patients with left main disease who have survived the early postoperative period are similar to those in three-vessel disease (fig. 6).

Figure 3 is a plot of medically treated patients with three-vessel disease compared with the matched general population. The actuarial data on the surgical series include all categories of patients. In contrast, the VA Cooperative Study is highly selected, containing only patients with chronic stable angina pectoris. That may be one reason for the survival in that study being better than in the other three studies also shown at 4 years. At 4 years, the survival of the surgical patients in all categories was 4% less than that of the
matched population, while that for the VA medically treated patients is 21% less.

We have shown earlier that hospital mortality after surgical treatment in 1977 is not related to the number of distal anastomoses. Let us assume that hospital mortality is 0.9% (that of the entire group of patients operated upon in 1977 at our institution), or not significantly different between any of these categories of surgical patients. Assuming also that long-term results in patients being operated upon at present are at least as good in the years 1970–1979 (when the patients shown in the actuarial analyses were operated upon), we can compare projected 5-year survival of patients being operated upon today with that of the matched general population (table 4). The projection suggests that at the very least, surgical treatment eradicates the generally admitted poorer prognosis of patients with left main and three-vessel disease compared with that of patients with two-vessel disease, since the 5-year survival is not significantly different.

**Table 4. Comparison of Survival of Surgically Treated Coronary Artery Disease (University of Alabama, Birmingham) With Matched Population at 5 Years**

<table>
<thead>
<tr>
<th>Category</th>
<th>Surgical treatment* (± SEM)</th>
<th>Matched population</th>
<th>Significance level of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-vessel</td>
<td>93.9 ± 2.63</td>
<td>94.9</td>
<td>p = 0.7</td>
</tr>
<tr>
<td>2-vessel</td>
<td>87.6 ± 2.47†</td>
<td>95.0</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>3-vessel</td>
<td>88.9 ± 1.89†</td>
<td>95.0</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Left main</td>
<td>86.7 ± 3.90†</td>
<td>94.4</td>
<td>p = 0.05</td>
</tr>
</tbody>
</table>

*Hospital mortality assumed to be 0.9% for all categories.
†p for differences between these categories > 0.6.
among the three groups. The 5-year survival of these three groups is significantly less than that of the matched general population, but the differences are not great.

Is the Operation Affordable?

This also is a complex problem, and the answer depends upon both the resources of the patient or group or nation in question and the costs involved in the operation.

Many types of cardiac surgery are more expensive than coronary artery bypass grafting, including surgery for certain kinds of congenital heart disease, the neurosurgical treatment of certain intracranial processes, certain complex operations on the hand, renal transplantation and so forth. In fact, the discussion of affordability of coronary artery bypass grafting arises primarily because of the potentially large number of patients who might require the operation rather than from the inherent costs of the operation itself.

Research has already made the coronary artery surgery more affordable by making it more perfect and nontraumatic, so the patient can recover more quickly and thus less expensively. Most patients who undergo coronary artery bypass grafting in our unit now require an endotracheal tube and a ventilator for only 24 hours after the operation, and they leave the hospital for the 757 patients was a mean value of 8.98 ± 2.63 (SD) days. Thus, the need for expensive in-hospital care is not very different for patients who undergo coronary artery bypass grafting than for those who undergo such commonplace procedures as gastrectomy and pneumonectomy, and considerably less than for those who have a hip replacement or renal transplant.

True evaluation of the costs of surgical intervention compared with those of years of medical treatment would be interesting. Even the costs to the individual and to society of no treatment, an option our society could consider, might be as great as those of surgical treatment.

These problems must be examined. Rhetoric, premature public announcements and sweeping generalizations can only delay our true understanding of these complex problems.

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References


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