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CLINICAL STUDIES

Young Adults With Coronary Atherosclerosis: 10 Year Results of Surgical Myocardial Revascularization

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This study reviews data on 107 patients, aged 35 years or younger, who underwent surgical coronary revascularization from 1971 to 1975. Early clinical events included one operative death and five nonfatal perioperative myocardial infarctions. Late follow-up (mean interval after operation 115 months) demonstrated actuarial survival rates of 94% at 5 years and 85% at 10 years. Fifteen late deaths, 23 nonfatal myocardial infarctions, 13 reoperations and return of severe angina in 10 patients were considered late clinical events. Actuarial survival free of early or late clinical events was 77% at 5 years and 53% at 10 postoperative years. Testing of clinical, angiographic and operative variables for influence on survival and event-free survival showed that survival was decreased by multivessel disease and impaired left ventricular function; event-free survival was decreased by a family history of coronary disease and cigarette smoking. Both survival and event-free survival were decreased by diabetes and elevated serum cholesterol.

Postoperative cardiac catheterization (64 patients, mean postoperative interval 47 months) demonstrated that mammary artery graft patency (25 of 27, 93%) exceeded vein graft patency (49 of 88, 56%, $p < 0.01$). The atherogenic diatheses of young adults may compromise the operative result, whereas use of internal mammary artery grafts may enhance the palliation of bypass surgery.

Coronary atherosclerosis in young adults represents a poignant challenge to current therapy. Not only may angiographic demonstration of critical coronary lesions define an immediate threat to survival, but there is also concern that early onset coronary artery disease may be an indicator of rapidly progressing atherosclerosis.

Coronary artery bypass grafting has been shown to be a safe and effective means of providing symptomatic palliation for most surgical candidates (1,2) and prolongation of survival for some subgroups of patients with coronary atherosclerosis (3,4). The application of bypass grafting to young adults seems desirable from many standpoints. The vigorous life-style of young adults makes them intolerant of anginal symptoms. Perioperative mortality, which increases with age, is low for young patients (5), but it is the long-term results that are crucial. The low level of mortality from noncardiac causes in this age group implies that large increases in life span may be achieved if cardiac disease can be controlled. However, coronary bypass surgery does not halt progression of atherosclerosis, and a malignant atherogenic diathesis might compromise the effectiveness of revascularization in young adults. A high prevalence of coronary risk factors such as hyperlipidemia, hypertension, smoking and a family history of coronary disease has been documented (6–11) in groups of young adults with clinically and angiographically documented coronary atherosclerosis, although conflicting data exist regarding the influence of those coronary risk factors on the prognosis and rate of angiographic progression of coronary artery disease (12–19).

Therefore, the young adult with symptomatic coronary artery disease presents us with a distillate, not only of our hopes for direct revascularization but also of our fears regarding the compromise of its palliation by the progressive nature of atherosclerosis. The goals of this study were to document the natural history of young adults after coronary bypass grafting, and highlight the influence of preoperative coronary risk factors by examining a group of patients with a high risk factor prevalence.

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Methods

Selection of patients. With the aid of a computerized cardiovascular information registry, all Cleveland Clinic Foundation patients aged 35 years or younger undergoing primary isolated direct coronary revascularization during 1970 to 1975 were identified. These years were chosen to provide adequate follow-up. Two foreign patients were excluded because of anticipated follow-up difficulties. The study group consisted of 107 patients. Preoperative, operative and perioperative data were obtained from hospital records. Follow-up was by telephone interviews with all surviving patients, routine mail questionnaires sent to surviving patients and, when interim events had occurred, contact with the patient's personal physician. Five survivors were lost to detailed follow-up after contact in late 1981, although three are known to be still alive. All other survivors were contacted in May or June 1983.

Angiographic analysis. Preoperative angiographic data were obtained from the review of preoperative films by Cleveland Clinic Foundation cardiologists.

For patients who had postoperative cineangiographic studies, the preoperative and postoperative cineangiograms were reviewed together by a single cardiologist. Twenty-six arterial segments of the native coronary circulation were analyzed and obstructive lesions were recorded (14). For determination of progression of disease between the preoperative and postoperative studies, the proximal segments of grafted arteries were excluded from consideration. If a new occlusion or a 20% or greater decrease in luminal diameter was noted in either ungrafted arteries or in distal segments of grafted arteries, progression of native coronary disease was said to be present. The postoperative study of one patient was not available for review and the patient was excluded from the analysis of native coronary disease progression, although graft patency data were included.

Analysis of coronary risk factors. The term "coronary risk factors" refers to factors thought to be associated with atherogenesis: hypercholesterolemia, hypertriglyceridemia, diabetes, hypertension, cigarette smoking and a family history of coronary artery disease. Patients were considered to have these risk factors if they were present at the time of operation. Subsequent risk factor modification was not evaluated. *Definitions of individual risk factors were as follows*:

Hypercholesterolemia. Twelve hour fasting cholesterol determinations were obtained using the ferric chloride-sulfuric acid method through May 1974 and by the Liebermann-Burchard method since that time. Hypercholesterolemia refers to a cholesterol level greater than 300 mg/dl.

Hypertriglyceridemia. Twelve hour fasting levels greater than 180 mg/dl were considered abnormal.

Diabetes. Patients were classified as having diabetes if they had an abnormal glucose tolerance test or history of management with diet, oral agents or insulin.

Hypertension. Hypertension was defined as a diastolic blood pressure of 90 mm Hg or greater as determined by the admitting physician and on at least two other occasions by the nursing staff. A history of treatment for the condition was not considered necessary for the diagnosis, although normotensive patients receiving treatment were considered to have hypertension.

Cigarette smoking. All smokers admitted to smoking at least one pack of cigarettes per day for the previous year. Previous smokers who had not smoked for 1 year before operation were considered nonsmokers.

Family history of coronary artery disease. A family history was defined as a history of angina, myocardial infarction or sudden death for either parent or siblings, an inclusive definition.

Statistical analysis. The chi-square test was used to test univariate associations. Univariate analyses of survival time and event-free survival time were obtained using Kaplan-Meier curves to handle censored observations, and the generalized Wilcoxon statistic (20) was used to test for curve differences. After identification of potentially influential variables, multivariate analyses were carried out utilizing stepwise Cox proportional hazards linear model procedures (see Appendix).

Results

Preoperative and operative data. The 107 study patients included 96 men and 11 women; the mean age was 32.6 years (median 33, range 26 to 35). Distribution of preoperative functional class, graded according to New York Heart Association criteria (21), was class I, 11 patients (10.3%); class II, 65 patients (60.7%); class III, 22 patients (20.6%) and class IV, 9 patients (8.4%).

Table 1 shows preoperative coronary risk factors, the

Table 1. Preoperative Risk Factors

Risk Factor	No. of Patients	% of Patients
	Incidence of Risk Factors	
Family history	71	66.4
Smoking	90	84.1
Diabetes	6	5.6
Hypertension	23	21.5
Hypercholesterolemia	21	19.6
Hypertriglyceridemia	62	57.9
No. of Risk Factors Present	Distribution of Risk Factors	
1	9	8.4
2	25	23.4
3	36	33.6
4	23	21.5
5	11	10.3
6	3	2.8

proportion of the group possessing each risk factor and patients grouped according to the number of risk factors present. Seventeen patients (15.9%) had both hypertriglyceridemia and hypercholesterolemia. Of the six patients with diabetes, two were managed with insulin, one with oral agents and three with diet.

Table 2 shows the preoperative angiographic characteristics of the study group in terms of left ventricular function and the number of vessels judged significantly (≥ 70%) obstructed. Three patients had left main coronary stenoses of 50, 70 and 90%, respectively. Left ventricular function was graded according to segmental impairment on the basis of seven left ventricular segments. There was an association between the number of preoperative risk factors present and the number of vessels diseased because patients with one, two or three risk factors present had predominantly single vessel disease and those with four, five or six risk factors had predominantly multivessel disease ($p = 0.0006$).

Operation was carried out with normothermic cardiopulmonary bypass, and anoxic arrest was used for production of a clear surgical field. One hundred thirty-four saphenous vein grafts and 52 internal mammary artery grafts were performed, an average of 1.74 grafts per patient. Forty-eight patients received one, 41 received two and 18 received three or more bypass grafts. One hundred five grafts were performed to the left anterior descending system (including diagonal branches), 36 to circumflex vessels and 45 to the right coronary artery system. If all primary and secondary vessels obstructed 70% or more and perfusing viable myocardium were bypassed, the patient was considered to have had complete revascularization. By this definition, 83 patients (77.6%) had complete revascularization.

The one death in the perioperative period was caused by myocardial infarction and ventricular arrhythmias. Five patients had a nonfatal perioperative myocardial infarction. Criteria for perioperative myocardial infarction were new Q waves and cardiac enzyme elevation in three patients and cardiac enzyme elevation alone in two. Other perioperative morbid events included reoperation for bleeding (six patients) and transient neurologic deficits (two patients).

Table 2. Preoperative Angiographic Characteristics

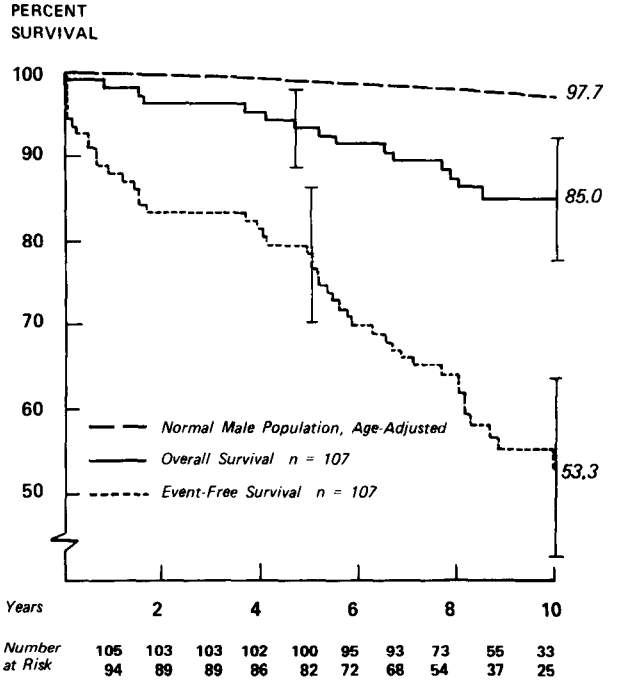
	No. of Patients	% of Patients
Extent of disease (major vessels ≥ 70% obstruction)		
Single vessel	40	37.4
Double vessel	48	44.8
Triple vessel	19	17.8
Left ventricular function		
Normal	75	70.1
1 segment impaired	25	23.4
2 segments impaired	7	6.5

Late follow-up. *Mortality and survival.* The mean (± SD) interval from operation to latest follow-up of survivors averaged 115 ± 17 months (range 65 to 147). Fifteen late deaths occurred. Three were due to noncardiac causes: suicide at 10 months, lung cancer at 19 months and trauma at 96 months. Of the cardiac deaths, one was due to autopsy-documented pulmonary embolism at 49 months. Other late cardiac deaths occurred 19 to 133 months after operation; six were associated with clinical myocardial infarction, one was due to congestive heart failure and five were sudden but occurred out of the hospital. Combining the late deaths with the cardiac operative death yields a total of 16 deaths, 13 cardiac and 3 noncardiac. Overall survival was 94% at 5 years and 85% at 10 years (Fig. 1).

Cardiac reoperation. Thirteen patients underwent cardiac reoperation at a mean interval of 81 months after the primary procedure. One patient received an aortic valve replacement 82 months after revascularization. Angiographic indications for reoperative revascularization were progression of disease in the native circulation alone in 1 patient after a 10 month interval, graft occlusion alone in 1 patient at a 98 month interval and a combination of progression of disease in the native circulation and graft occlusion in the remaining 10 patients at 30 to 119 months after primary revascularization. The clinical indication for reoperation was return of angina in all patients.

Late myocardial infarction. The diagnosis of probable late nonfatal myocardial infarction was made in 23 patients

Figure 1. Survival (Kaplan-Meier) and event-free survival of the study group compared with the expected survival of an age-matched sample of men from the United States population (22).



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after primary revascularization at intervals ranging from 3 to 121 months (mean 64 ± 36). Criteria for the diagnosis of myocardial infarction were hospitalization with permanent electrocardiographic changes, a characteristic clinical episode associated with cardiac enzyme elevation or a clinical episode with subsequent catheterization demonstrating a new segmental wall motion abnormality. Electrocardiograms at late follow-up were not available for all patients.

Functional states. Symptoms of survivors were graded according to New York Heart Association criteria. At latest follow-up, 59 patients (65%) were in class I, 22 were in class II (24%) and 10 (11%) reported class III or IV symptoms. Sixty-five patients work full-time outside the home or have been laid off from full-time employment. Five work full-time within the home, 19 have received medical disability and 2 fully active patients have declined employment. Sixty-eight (75%) consider themselves fully active with no limits, 19 (21%) feel limited in some way and 4 (4%) consider themselves disabled.

Event-free survival. To provide an index of postoperative course more encompassing than survival alone, event-free survival was also examined. Event-free survival was defined as survival without the occurrence of a clinical event. Early clinical events were defined as death or perioperative myocardial infarction. Late clinical events were defined as death, late nonfatal myocardial infarction, cardiac reoperation or return of class III or IV symptoms. Forty-eight patients experienced events; 59 did not. Event-free survival was 77% at 5 and 53% at 10 postoperative years (Fig. 1).

Determinants of survival and event-free survival. Twelve variables tested for their association with survival by means of univariate analyses followed by multivariate analyses were: gender, age (continuous variable), family history of coronary artery disease, smoking, hypertension, diabetes, hypercholesterolemia (examined both as a continuous and as a dichotomous variable, >300 versus ≤300 mg/dl), hypertriglyceridemia, left ventricular function (normal versus impaired), extent of disease (single vessel versus multivessel), use of mammary artery graft and complete revascularization. Diabetes, although involving only six patients (four deaths), had a strong adverse influence on survival ($p < 0.001$). Because of the disproportionate influence of this variable, diabetes was not tested in the multivariate model, and a stratified proportional hazards model was used to adjust for its effect (see Appendix). The natural logarithmic transformation of preoperative serum cholesterol was used to adjust for the wide range of cholesterol values (135 to 871 mg/dl).

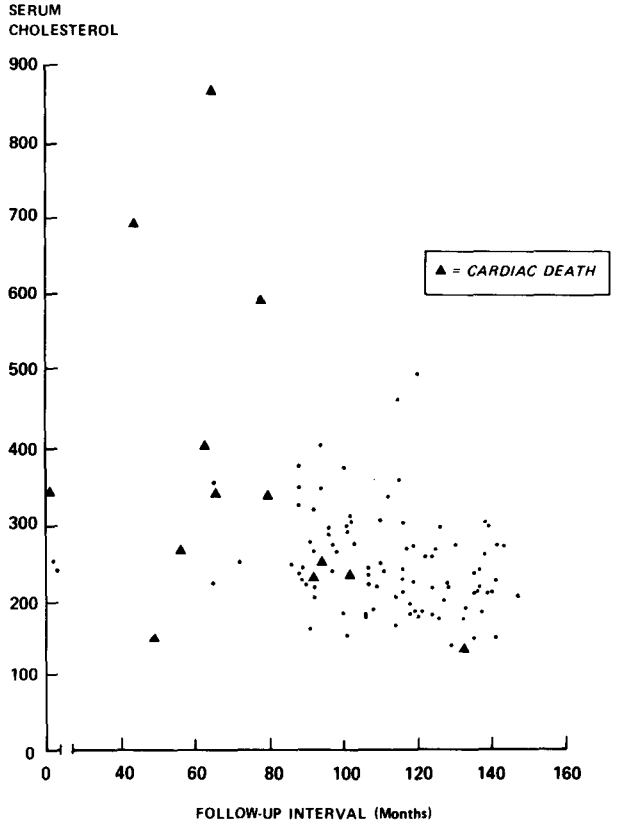
Results of this Cox regression model demonstrated that, in addition to diabetes, other factors having an adverse influence on survival were abnormal left ventricular function, increased serum cholesterol and multivessel coronary disease (Table 3). Exclusion of noncardiac deaths did not significantly alter those results. When tested as a dichotomous variable, elevated cholesterol still had a strong univariate influence on survival ($p = 0.006$), which was confirmed with multivariate testing. Figure 2 details the relation between serum cholesterol and cardiac death. The combination of hypercholesterolemia and hypertriglyceridemia did not

Table 3. Multivariate Analyses of the Influence of Preoperative and Operative Variables

Variable	p Value	Relative Risk* of Death or Event
	Survival	
LV function (impaired)	0.001	6.0
Cholesterol (ln)	0.022	7.1
Extent of disease (single vessel)	0.044	0.2
	Event-Free Survival	
Cholesterol (ln)	0.002	3.7
Family history	0.004	3.2
Smoking	0.011	4.0
LV function (impaired)	0.007	2.4

*For every unit increase in the variable, the risk of death (or event) increases by this factor, given that the other variables in the model remain constant. ln = natural logarithmic function; LV = left ventricular.

Figure 2. Preoperative serum cholesterol levels plotted against follow-up interval. **Triangles** indicate patients dying of cardiac causes.



have a predictive value greater than that of hypercholesterolemia considered alone.

The same 12 variables were examined for their influence on event-free survival. Diabetes had a strong negative influence on event-free survival ($p < 0.03$), as only one diabetic patient survived without an event (Fig. 3). Again, the influence of diabetes was so strong and involved so few patients that it was removed from the multivariate model which was then stratified for diabetes. Results of that multivariate model (Table 3) also identified the coronary risk factors of serum cholesterol (whether examined as a continuous or dichotomous variable), family history and smoking as influential (Fig. 3), in addition to the angiographic variable of left ventricular function (Fig. 4).

Postoperative angiographic data. *Vein graft patency.* Sixty-four patients underwent at least one postoperative catheterization (mean postoperative interval 47 months, range 2 to 125). Defining a "patent" graft as one without a stenosis of 50% or greater, 49 (56%) of 88 saphenous vein grafts were patent compared with 25 (93%) of 27 internal mammary artery grafts ($p < 0.01$). Of the 39 nonpatent vein grafts, 33 were totally occluded and 6 had hemodynamically significant stenoses of 50 to 90%. Eight of the 49 patent vein grafts had angiographic irregularities or stenoses of less than 50%.

Table 4 shows the number of grafts studied and the number patent without significant stenoses according to the coronary vessel grafted and the type of graft. For patients studied at a postoperative interval of less than 24 months, 28 (71%) of 41 vein grafts were patent; 2 of the 28 patent grafts had angiographic irregularities. Of 47 vein grafts in patients studied 24 or more months after operation, 21 (43%) were patent (although 6 of these grafts had angiographic irregularities or stenoses < 50%), 20 grafts were totally occluded and 6 had hemodynamically significant stenoses. Thus, 15 of the 47 vein grafts studied at 24 or more months were patent without any irregularity or stenosis. Vein graft patency at less than 24 months significantly exceeded vein graft patency at 24 or more months ($p < 0.05$). For mammary artery grafts, 14 of 14 were patent at less than 24 months and 11 of 13 were patent at 24 months or more. For 33 patients symptomatic at recatheterization, vein graft patency was 21 (41%) of 46 and mammary artery patency was 9 (82%)of 11, whereas for 31 patients asymptomatic at recatheterization, vein graft patency was 28 (67%) of 42 and mammary artery patency was 16 (100%) of 16. Vein graft patency of asymptomatic patients significantly exceeded that of symptomatic patients ($p < 0.05$).

Progression of coronary artery disease. Progression of disease in the native circulation was examined in the 63 patients whose postoperative studies were available for review. Progression was associated with postoperative interval, as it occurred in 32% (12 of 29) of patients who underwent cardiac catheterization at less than 24 postoperative months, and in 68% (26 of 34) restudied at 24 or more months ($p < 0.01$). Univariate analyses concerning the relations between coronary risk factors and progression in the native circulation demonstrated no significant correlations.

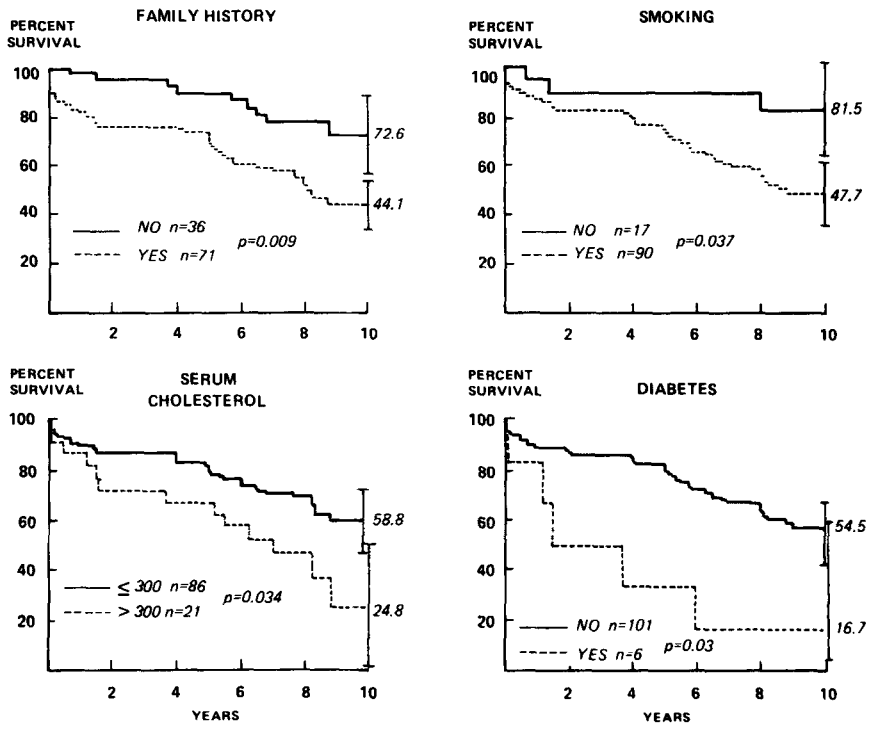


Figure 3. Univariate comparisons demonstrating the influence of four coronary risk factors on event-free survival (family history, smoking, serum cholesterol and diabetes).

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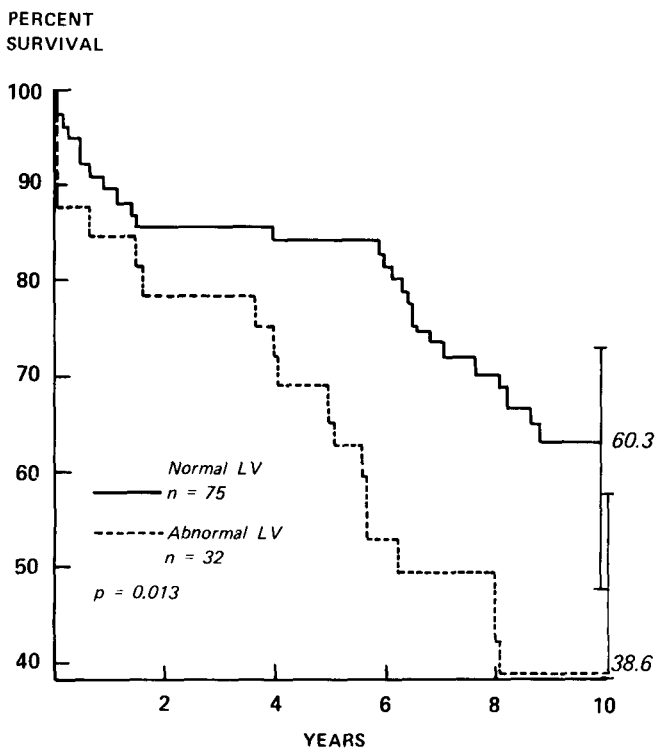

Figure 4. Event-free survival according to preoperative angiographic left ventricular (LV) function.

Discussion

Coronary atherosclerosis in the young adult. The relatively high prevalence of single vessel disease and normal left ventricular function in the patients in this study contrasts with our general series of patients undergoing revascularization from 1971 to 1975 (1), but it is consistent with other angiographic studies (10,23) of young adults with symptomatic coronary atherosclerosis. These angiographic findings may reflect the tendency for young, active patients with single vessel disease to experience symptoms. Furthermore, class II symptoms, perhaps tolerable to older individuals, are less acceptable to younger patients, a consideration in part responsible for the election of surgical therapy for many patients in the study group. These young adults also had a high risk factor prevalence. It is difficult to determine whether age of onset, independent of coronary risk factors, influences the prognosis of coronary artery disease. This study does not resolve that issue, because to do so requires large numbers of patients of different ages matched for multiple variables. This study does show that young adults continue to be at risk of death and cardiac complications, despite operation for myocardial revascularization. Older patients with surgically treated coronary atherosclerosis may have a survival approaching that of the age-adjusted "normal" population (24). These young adults did not. The 85% survival and 53% event-free survival rates at 10 years for this study group are inferior to the high survival rate and almost complete freedom from cardiac complications of the "normal" population, 35 years and younger (Fig. 1).

Table 4. Postoperative Graft Angiography

Coronary Vessel Grafted	Vein Grafts	Mammary Artery Grafts
Anterior descending	19 of 28 (69%)	21 of 22 (95%)
Diagonal	4 of 8 (50%)	1 of 1 (100%)
Circumflex	9 of 18 (50%)	3 of 4 (75%)
Right	17 of 25 (68%)	—
Total	49 of 88 (56%)	25 of 27 (93%)

Values indicate the number of grafts patent without stenosis of 50% or more/number studied (% patent).

Determinants of survival. The extremely young age of the patients in this study makes comparison with other published series inappropriate, but an examination of determinants of survival within this subgroup was enlightening. Many studies (1,12,24–26) involving patients either surgically or medically treated have shown left ventricular function and the number of stenotic vessels to be determinants of survival. Survival differences based on these variables are more pronounced for medical than for surgical patients, as bypass grafting reduces the number of effectively stenotic coronary vessels (1,12,24–26). As expected, left ventricular function and extent of disease influenced the postoperative clinical course of these young adults. However, coronary risk factors also influenced prognosis.

Role of coronary risk factors in prognosis. Diabetes and hypercholesterolemia decreased survival and event-free survival; smoking and a family history of coronary disease decreased event-free survival. Consideration of nonfatal events highlighted the effect of coronary risk factors, whereas angiographic variables were more influential when death alone was the end point. Coronary risk factors appear to be indicators of postoperative cardiac events, whereas the presence of abnormal left ventricular function or multivessel disease makes it more likely that those postoperative events will be fatal ones.

Despite evidence linking coronary risk factors to the occurrence of coronary artery disease (27,28), previous studies disagree regarding their relation to prognosis. For the placebo group of the Coronary Drug Project (18) comprising nonsurgical patients with clinical coronary artery disease, death was associated with smoking and hypercholesterolemia. However, study of medically treated patients with angiographically documented coronary atherosclerosis has failed to confirm those relations (26), even with a 15 year follow-up period reported by Proudfit et al. (12). Reviewing data on surgical patients, Hansen et al. (29) noted that patients with type II hyperlipoproteinemia had an increased in-hospital mortality rate and a higher risk over a 3 year follow-up period. Jones et al. (30) found diabetes to be associated with a slight decrease in postoperative survival over a 4 year follow-up period, and Hoffmann et al. (19) demon-

strated that a serum cholesterol level of 350 mg/dl or greater had a mild adverse influence on 5 year survival. Other surgical series (1,4,24,31,32) have not correlated prognosis and risk factors. Risk factors probably influence the long-term clinical course by promoting progression of atherosclerosis. The degree of progression is likely to be related to the intensity and duration of the atherogenic influence.

Relative to previous studies of surgical patients, our series involves a very young group of patients with a high prevalence of risk factors and extreme abnormalities of those risk factors, particularly in regard to juvenile diabetes and hypercholesterolemia. These considerations combined with the 10 year follow-up period made it possible for differences in the rate of progression of atherosclerosis to become apparent. Results of previous follow-up studies (33) of this patient group at a mean interval of 89 months showed a less precise correlation between risk factors and prognosis.

Risk factors correlated with progression of coronary disease and bypass graft failure. Anatomic causes of cardiac events include progression of atherosclerosis in the native circulation and bypass graft failure. Angiographic studies of patients not treated surgically differ regarding the influence of coronary risk factors on the progression of atherosclerosis in the native coronary circulation. Bemis et al. (15) and Nash et al. (17) found an association of hyperlipidemia and progression of atherosclerosis despite intervals between arteriographic studies averaging only 21 and 24 months, respectively. However, two large studies (13,14) of surgically treated patients with serial arteriograms failed to correlate native vessel disease progression with risk factors, identifying only the interval between arteriograms as a significant influence on disease progression.

Angiographic studies concerning surgical patients have correlated risk factors and graft failure; the longer the follow-up interval, the more that correlation has become apparent. Palac et al. (34) found that patients with stenotic vein grafts at 5 years after operation had higher average serum cholesterol and triglyceride levels than did control subjects. Data from the Montreal Heart Institute (35) indicate that stenoses occurring in vein grafts 7 to 12 years after operation were related to low density lipoproteins and low density beta-lipoprotein cholesterol, whereas stenoses occurring earlier were unrelated to risk factors. Our own recent review (36) of 501 patients undergoing serial arteriography showed that up to 5 years postoperatively, risk factors had no influence on graft status. Between 5 and 12 years after operation, vein graft failure correlated with hypercholesterolemia, hypertriglyceridemia and diabetes. In the present study, we were unable to document a correlation between risk factors and either graft occlusion or disease progression in the native circulation. However, only 60% of patients had undergone postoperative arteriography, decreasing the sample size available for evaluation, and many patients had undergone arteriography less than 2 years after operation, a point at which vein graft atherosclerosis cannot be expected to have had an impact.

Vein graft patency. Vein graft patency for these patients was not optimal. A review of our general series of revascularization patients operated on during 1971 to 1973 (1) documented an overall vein graft patency of approximately 80% at postoperative intervals of up to 7 years. For the young adults in the present study, the overall 56% vein graft patency and, particularly, the 43% patency of grafts studied more than 24 months after operation is cause for concern. Diffuse native coronary disease, abnormal platelet function in patients with hyperlipoproteinemia (37) and vein graft atherosclerosis may all have contributed to this high level of vein graft failure. The longer the postoperative interval at which arteriography was performed, the more vein graft attrition became apparent, as even among the 21 grafts considered patent at 2 or more years after operation, 6 had angiographic evidence of atherosclerosis. Kelly et al. (38) also found that patients operated on at age 40 or younger had inferior vein graft patency when compared with patients in their general revascularization series. It seems likely that the anatomic basis for the adverse effect of risk factors on the 10 year postoperative clinical course is an increase in vein graft atherosclerosis. That could not be documented in this study by a significant correlation between risk factors and graft occlusion. However, we do not have a continuous means of monitoring graft patency and the status of grafts at an early postoperative study is unlikely to correlate well with the occurrence of late clinical events.

Mammary artery graft patency. In contrast to vein grafts, the mammary artery grafts exhibited excellent patency. The advantage of mammary artery grafts has been demonstrated (5,35,39,40) for general groups of revascularization patients, but it is highlighted in these young adults by the inferior vein graft results. Because of the freedom of the mammary artery graft from atherosclerosis for up to 10 years after operation (5,35,38,39), the documentation of graft atherosclerosis in vein grafts followed up for more than 5 years after operation, the excellent long-term survival of patients receiving bilateral mammary artery grafts (41) and the observations of the current study, we use bilateral mammary artery grafts whenever possible for young adults undergoing revascularization.

Role of improved surgical techniques. The patients in the study group underwent operation a decade ago. The use of cardioplegia for myocardial protection since 1978 and improvements in anesthesia and surgical experience throughout the last decade have enabled surgeons to carry out more extensive procedures while maintaining a low perioperative risk. From 1976 to 1982, another 152 patients, aged 35 years or younger, underwent coronary bypass grafting at the Cleveland Clinic Foundation with one operative death and three perioperative myocardial infarctions, while the average number of grafts per patient increased to 2.4

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and the proportion receiving mammary artery grafts increased to 69%. Currently, more than 90% of patients in this age group receive mammary artery grafts. In addition to extensive use of mammary artery grafts, including bilateral and sequential grafts, other operative techniques currently being employed include more complete revascularization and the use of multiple sequential vein grafts, although the specter of vein graft atherosclerosis makes the long-term results of those strategies uncertain.

Implications. Coronary atherosclerosis in young adults is a problem requiring long-term management. Myocardial revascularization resulted in a good symptomatic response, a high postoperative activity level and a reasonable 10 year survival. It is clear, however, that these patients were not "cured." Risk factor modification was not evaluated, and it is self-evident that that strategy should be pursued postoperatively even though its efficacy has not been demonstrated in postoperative patients. Recent data (42,43) suggest that early vein graft patency might be enhanced by platelet inhibitors, and their use in young adults seems indicated although their influence on late vein graft failure is not known. The internal mammary artery is the bypass graft of choice for young adults.

Appendix

Statistical Methods

Multivariate analyses of survival and event-free survival were based on the Cox proportional hazards regression model (44) (BMDP2L [45]). This analysis, which presumes that death (event) rates may be modeled as log-linear functions of the covariates, allows one to quantify and test the relation between survival and a set of explanatory variables.

In particular, a stratified, stepwise proportional hazards model was used. The analysis was stratified for diabetes to accommodate the fact that the ratio of the hazard rates for the diabetic patients compared with the nondiabetic patients was not constant over time. With stratification, the model is modified to allow the arbitrary hazard function $h_{oj}(t)$ to be different in each stratum while the regression coefficients are the same across strata (46):

$$h_j(t; \underset{\sim}{z}) = h_{oj}(t) \exp(\beta' \underset{\sim}{z}),$$

where $h_j(t; \underset{\sim}{z})$ is the hazard rate at time t for an individual with covariate vector $\underset{\sim}{z}$; β is a vector of unknown regression coefficients; and $h_{oj}(t)$ is an unknown hazard function for an individual with covariate vector $\underset{\sim}{z} = O$; with j representing one of s different strata.

Stepwise indicates the process by which the explanatory variables were selected for entry into the model. This process allows a subset of independent variables significantly related to survival to be selected from a larger number of independent variables under consideration.

Nine possible risk factors (covariates) were considered for inclusion in the model. Cholesterol and age were included as continuous variables. Preoperative left ventricular function, extent of disease, extent of revascularization, history of coronary artery disease, smoking, hypertension and elevated triglycerides were used as categoric variables. Sets of indicator variables were created for those factors with more than two categories. Each covariate was tested for its contribution to the model by means of a likelihood ratio method. The most significant covariate is entered into the model assuming it meets the tolerance level for inclusion ($p \leq 0.10$). Significant levels are recalculated for the remaining covariates, given that the first variable is already in the model. The next most significant variable is entered and so on, until no further covariates meet the entry criteria. If at any time the significance level of a covariate decreases to below 0.15 because of the inclusion of other variables, it is dropped from the model.

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