The impact of placing multiple grafts to each myocardial territory on long-term survival after coronary artery bypass grafting

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Objective: Incomplete myocardial revascularization decreases survival for patients undergoing coronary artery bypass grafting. The effects of constructing multiple grafts to each major diseased artery territory are unknown. We aimed to determine the impact on long-term survival after coronary artery bypass grafting of placing multiple grafts to each myocardial territory.

Methods: We reviewed data from 1129 consecutive patients who underwent coronary artery bypass grafting at our institution between 1997 and 2007 and compared outcomes between patients who received multiple grafts to each major diseased artery territory (n = 549) with those of patients who received single grafts to each territory (n = 580). We assessed long-term survival with Kaplan–Meier curves generated by log-rank tests, adjusting for confounding factors with Cox proportional hazards regression analysis.

Results: Patients who received multiple grafts to each major diseased artery territory had longer cardiopulmonary bypass and aortic crossclamp times than patients who received single grafts per territory. Patient groups had similar early outcomes, including 30-day mortalities (1.3% vs 1.4%, $P > .999$) and incidences of major adverse cardiac events (2.9% vs 2.2%, $P = .57$). Cox regression 10-year survival curves were also similar between groups (adjusted hazard ratio 0.94, 95% confidence interval 0.67–1.34, $P = .74$).

Conclusion: Patients who received multiple grafts to each major diseased artery territory had early outcomes similar to those who received single grafts per territory. Constructing multiple grafts to each major diseased artery territory increases operative time and does not improve long-term survival.

There are more than 13 million people with coronary artery disease (CAD) in the United States.[1] Many of these people have multivessel CAD, which is best treated with coronary artery bypass grafting (CABG).[2] For this reason, CABG is the most commonly performed procedure for cardiac surgeons. More than 150,000 CABG operations annually have been performed nationwide since the 1990s.[3] One of the advantages of CABG relative to percutaneous coronary intervention (PCI) is that CABG allows complete myocardial revascularization in a single procedure.

Complete myocardial revascularization, which has long been the standard for CABG procedures, is traditionally defined as a single graft to each major diseased artery system.[4] Numerous studies have shown incomplete revascularization to be deleterious in terms of overall survival for patients undergoing CABG.[5-8] Previous studies have used various definitions of complete revascularization, however, and no single definition is universally accepted at present.

With data from the Bypass Angioplasty Revascularization Investigation trial, Vander Salm and colleagues[4] attempted to derive the optimum definition of complete revascularization in CABG by evaluating the utility of four different definitions in predicting long-term outcomes: (1) traditional complete revascularization, with a single graft to each major diseased artery system; (2) functional complete revascularization, with a single graft to all diseased major or primary segmental vessels; (3) a number of distal anastomoses greater than or equal to the number of diseased coronary segments; and (4) a number of distal anastomoses to the major coronary systems greater than or equal to 1. In doing so, Vander Salm and colleagues[4] concluded that construction of multiple grafts to any coronary artery system other than the left anterior descending may not be advantageous. Because all patients in the Bypass Angioplasty Revascularization Investigation trial were required to be clinically suitable for PCI, however, patients with the most severe and extensive disease were ineligible for the study. The conclusion of that study therefore may not be applicable to patients with complex and severe CAD.

Although incomplete myocardial revascularization has been shown to decrease overall survival for patients with CAD, little is known about the effects of placing multiple grafts to each major diseased artery territory in these patients. It may be logical to hypothesize that constructing more grafts to each major diseased artery territory improves

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CAD	= coronary artery disease
CICSP	= Continuous Improvement in Cardiac Surgery Program
MEDVAMC	= Michael E. DeBakey Veterans Affairs Medical Center
PCI	= percutaneous coronary intervention
VA	= Department of Veterans Affairs

survival for patients with CAD. The aim of our study therefore was to examine the impact on long-term survival in patients undergoing CABG of placing multiple grafts to each major diseased artery territory.

MATERIALS AND METHODS

Patient Population

The study was granted a waiver of consent and approved by the institutional review boards at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) and Baylor College of Medicine, Houston, Tex. Data were obtained from the MEDVAMC's Continuous Improvement in Cardiac Surgery Program (CICSP) database and from retrospective review of the computerized patient record system. Computerized operative reports and coronary catheterization reports were reviewed for each patient to determine the location of each bypass graft and the degree and location of coronary artery stenosis. The CICSP database, organized by the Department of Veterans Affairs (VA) to provide continuous assessment and improvement of quality of care for all patients who undergo cardiac surgery in VA hospitals, contains comprehensive data on more than 140 variables (including demographic, clinical, outcome, and resource variables) collected prospectively at prespecified times from all cardiac surgical patients in the VA Health Care System.[9]

Data in the CICSP database were collected by a research nurse through reviews of each patient's computerized medical record. The death index component of the CICSP database was obtained from the Beneficiary Identification Records Locator Subsystem death file. The Beneficiary Identification Records Locator Subsystem is a Veterans Benefits Administration database containing records of all beneficiaries, including veterans whose survivors have applied for death benefits. In addition to these applications for VA benefits, sources of data include veterans discharged from military service since March 1973, Medal of Honor recipients, and service members with accounts for VA education benefits. The Beneficiary Identification Records Locator Subsystem death file contains information on veterans known to be deceased from any cause. The file can be linked to other files by the veteran's real or scrambled social security number. A weekly match process with the Social Security Administration Death Master File or a notification from a hospital, cemetery, or relative or acquaintance causes a veteran's death to be automatically noted in the file. Each January (starting in 2004), this file is refreshed with a baseline file from the Veterans Benefits Administration to ensure data accuracy by removal of records that may have been added to the file erroneously.

From the CICSP database, we identified 1129 consecutive patients who underwent primary isolated CABG at the MEDVAMC between October 1, 1997, and March 31, 2007. We excluded patients who underwent CABG without cardiopulmonary bypass, patients who underwent CABG concomitantly with other cardiac surgical procedures, patients with previous heart operations, and patients with incomplete myocardial revascularization. One hundred thirteen patients were excluded from the study because of incomplete myocardial revascularization. The most commonly documented reason for incomplete revascularization was inadequate coronary artery target size or severely diseased coronary artery targets.

Data analyzed for each patient included age, sex, number of bypass grafts, number and location of coronary artery stenoses, cardiopulmonary bypass and aortic crossclamp times, current tobacco smoking status, New York Heart Association functional class, Canadian Cardiovascular Society angina class, body mass index, preoperative albumin and creatinine levels, extent of CAD, previous PCI within 3 days of surgery, previous myocardial infarction, and history of chronic obstructive pulmonary disease, peripheral vascular disease, cerebral vascular disease, and diabetes.

We used the traditional definition of complete revascularization for the purpose of this study. Patients were considered to have complete revascularization if at least one graft was placed in each major diseased artery territory. The left anterior descending/diagonal, the circumflex/ramus, and the right coronary arteries were considered the three major coronary artery territories. Major CAD or stenosis was defined as a reduction of more than 50% in luminal diameter in any of the following three major artery territories: left anterior descending/diagonal, circumflex/ramus, or right coronary arteries.

Patients were divided into two groups: those with single grafts to each major diseased artery territory (n = 580, single-graft group) and those with multiple grafts to each major diseased artery territory (n = 549, multiple-graft group). All patients in our selected cohort received at least one graft to each major diseased artery territory. The decision to construct more grafts was at the discretion of the individual surgeon.

Study End Points

All study end points used in this analysis were specified in advance. The primary end points were all-cause 30-day and late mortalities. The secondary end points were the incidences of postoperative stroke, renal failure requiring dialysis, mediastinitis, and reexploration for bleeding; the duration of postoperative ventilator support; and the 30-day perioperative rate of major adverse cardiac events, which included perioperative myocardial infarction, cardiac arrest requiring cardiopulmonary resuscitation, and the need for new mechanical circulatory support. Perioperative myocardial infarction was considered to have occurred if any of the following diagnostic criteria were met: evolutionary ST-segment elevations, new Q waves in two or more contiguous electrocardiographic leads, or a new left bundle branch block pattern on the electrocardiogram. New mechanical circulatory support was defined as the postoperative initiation of support with an intra-aortic balloon counterpulsation pump, extracorporeal membrane oxygenation, a ventricular assist device, or any combination of these devices. Postoperative stroke was considered to have occurred if there was any new objectively determined neurologic deficit that lasted more than 72 hours and that appeared in the immediate postoperative period or within 30 days after surgery.

Statistical Analysis

Data from categorical variables were summarized as frequencies (percentages), which were compared between groups with the χ^2 test or the Fisher exact test. Data from continuous variables were summarized as mean ± SD and compared between groups with the Student *t* test after the data were confirmed to be normally distributed. Kaplan–Meier survival curves were generated, and a log-rank test was performed to find statistical differences. To determine whether placing multiple grafts to each major diseased artery territory independently predicts long-term survival, Cox proportional hazards regression analysis was used to control for confounding covariates in the forward stepwise regression model. Potential confounding covariates included in the model were age, sex, cardiopulmonary bypass and aortic crossclamp times, current tobacco smoking status, New York Heart Association functional class, Canadian Cardiovascular Society angina class, body mass index, preoperative albumin and creatinine levels, extent of CAD, previous PCI within 3 days of surgery, previous myocardial infarction, and histories of cerebrovascular disease, diabetes, peripheral

TABLE 1. Preoperative patient characteristics

	Patients with 1 graft (n = 580)	Patients with >1 graft (n = 549)	*P* value
Age (y, mean ± SD)	61.2 ± 8.2	62.1 ± 8.3	.07
Male sex (No.)	575 (99.1)	547 (99.6)	.29
Body mass index (kg/m^2, mean ± SD)	29.4 ± 5.5	29.2 ± 5.3	.52
Preoperative albumin (g/dL, mean ± SD)	3.7 ± 0.4	3.6 ± 0.4	.24
Preoperative creatinine (mg/dL, mean ± SD)	1.2 ± 0.4	1.2 ± 0.7	.41
Current tobacco smoker (No.)	221 (38.1%)	188 (34.2%)	.19
Peripheral vascular disease (No.)	201 (34.7%)	156 (28.4%)	.03
Cerebral vascular disease (No.)	131 (22.6%)	112 (20.4%)	.39
Diabetes (No.)	226 (39.0%)	232 (42.3%)	.28
Left main coronary artery disease (No.)	233 (40.2%)	174 (31.7%)	.003
Triple-vessel coronary artery disease (No.)	386 (66.6%)	289 (52.6%)	<.0001
Chronic obstructive pulmonary disease (No.)	222 (38.3%)	174 (31.7%)	.02
Canadian Cardiovascular Society angina class III or IV (No.)	423 (72.9%)	268 (67.0%)	<.0001
New York Heart Association functional class III or IV (No.)	211 (36.4%)	203 (37.0%)	.84
Previous myocardial infarction (No.)	388 (66.9%)	359 (65.4%)	.62
Previous percutaneous coronary intervention within 3 d (No.)	6 (1.0%)	2 (0.4%)	.29

vascular disease, and chronic obstructive pulmonary disease. All statistical analyses were performed with SPSS version 15.0 software (SPSS Inc, Chicago, Ill).

RESULTS

The two groups of patients did not differ significantly in terms of preoperative demographic data (Table 1). Peripheral vascular disease and chronic obstructive pulmonary disease were, however, slightly more prevalent among patients who received single grafts to each major diseased artery territory (single-graft group) than among those who received multiple grafts to each major diseased artery territory (multiple-graft group). Additionally, a greater percentage of patients in the single-graft group were in Canadian Cardiovascular Society angina class III or IV. Coronary artery disease was more extensive in the single-graft group. Overall, the two groups of patients were comparable with regard to demographic data and comorbidities.

TABLE 2. Intraoperative and postoperative characteristics

	Patients with 1 graft (n = 580)	Patients with >1 graft (n = 549)	*P* value
Cardiopulmonary bypass time (min, mean ± SD)	102.5 ± 27.0	124.0 ± 36.1	<.0001
Aortic crossclamp time (min, mean ± SD)	56.6 ± 17.0	69.9 ± 20.4	<.0001
No. of venous grafts (mean ± SD)	1.6 ± 0.6	2.4 ± 0.8	<.0001
No. of internal thoracic arterial grafts (mean ± SD)	0.9 ± 0.3	0.9 ± 0.3	.09
Renal failure (dialysis, No.)	6 (1.0%)	9 (1.6%)	.44
Stroke (No.)	12 (2.1%)	11 (2.0%)	>.999
Reexploration for bleeding (No.)	6 (1.0%)	7 (1.3%)	.79
Mediastinitis (No.)	7 (1.2%)	6 (1.1%)	>.999
Mechanical ventilation >48 h (No.)	37 (6.4%)	44 (8.0%)	.30

Intraoperative and postoperative measures are shown in Table 2. Not surprisingly, the single-graft group had significantly shorter cardiopulmonary bypass times (102.5 ± 27.0 min vs 124.0 ± 36.1 min, $P < .0001$) and aortic crossclamp times (56.6 ± 17.0 min vs 69.9 ± 20.4 min, $P < .0001$) than did the multiple-graft group. The incidences of postoperative renal failure requiring dialysis, stroke, mediastinitis, reexploration for bleeding, and ventilator dependence for longer than 48 hours were similar between the groups.

There were no significant differences in 30-day mortality and the rate of major adverse cardiac events between the single-graft and multiple-graft groups (Figure 1). Kaplan–Meier survival curves for the two groups of patients were generated from all-cause mortality and censored data. Cox proportional hazards regression analysis was used to adjust for potential preoperative and intraoperative confounding factors (Tables 1 and 2). The mean follow-up period for the cohort was 5.3 years (range 0–10 years). A total of 79 patients (49 in the single-graft group and 30 in the multiple-graft group) were included as the number of patients at risk for the analysis at 9-year survival, as illustrated in Figure 2. The Cox regression survival curves (Figure 2) showed that, independent of other predictors, the use of a single graft and the use of multiple grafts produced similar long-term survivals. Specifically, the 9-year survivals were 78.4% ± 2.7% (mean ± SEM) for the single-graft group and 78.8% ± 3.5% for the multiple-graft group; the adjusted hazard ratio was 0.94 (95% confidence interval 0.67–1.34, $P = .74$).

DISCUSSION

Hemodynamically significant coronary artery stenosis decreases blood perfusion to the myocardial muscle, thereby

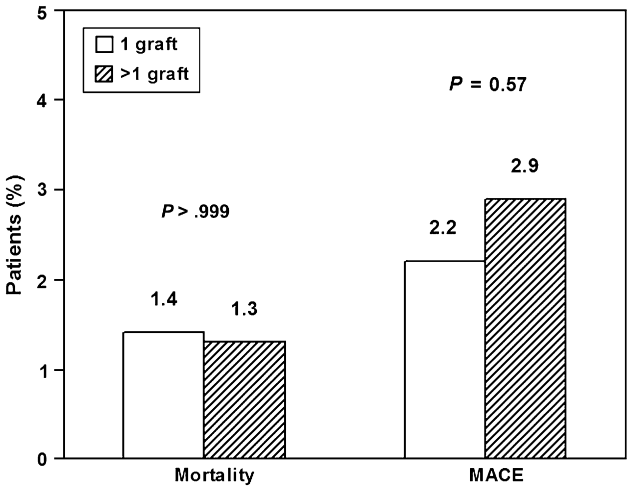

FIGURE 1. Mortality and rate of major adverse cardiac events *(MACE)* within 30 days of operation among patients with single grafts to each major diseased artery territory and patients with multiple grafts to each major diseased artery territory.

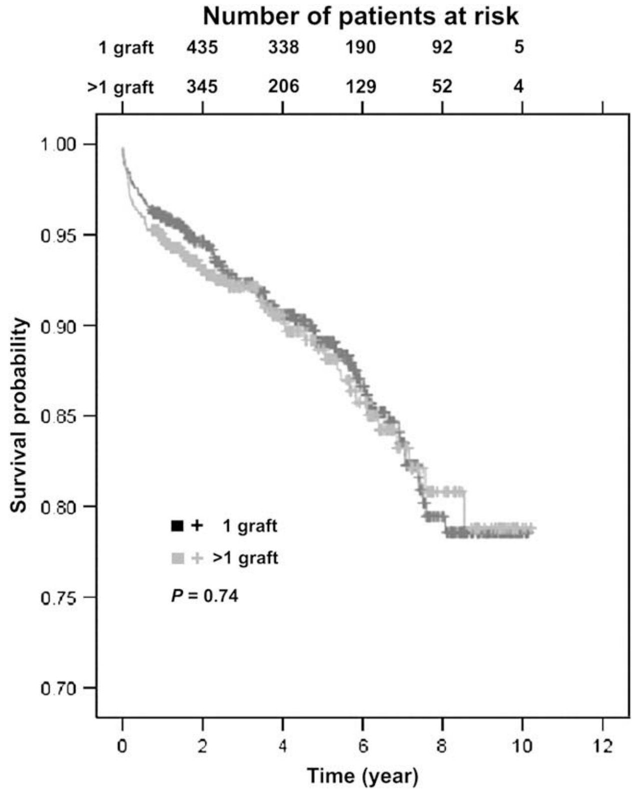

FIGURE 2. Survival curves after coronary artery bypass grafting for patients with single grafts to each major diseased artery territory and patients with multiple grafts to each major diseased artery territory.

causing ischemia and angina pectoralis.[10] Coronary artery bypass grafting aims to increase blood flow to areas of the myocardium beyond the critical stenosis. Complete myocardial revascularization has long been the criterion standard in CABG. Several large studies have established a long-term survival benefit of complete revascularization relative to incomplete revascularization in cardiac surgical patients.[5-8] The ability to achieve complete revascularization in a single setting is one of the major advantages of CABG relative to PCI. Furthermore, PCI is only able to increase blood flow to a single coronary artery beyond each stented critical stenosis, whereas CABG has the possibility of constructing multiple grafts to each area of critical stenosis if target vessels are reasonable in diameter. For the potential benefit of more blood flow, some surgeons choose to go beyond the traditional definition of complete revascularization when performing CABG and place multiple grafts to each major diseased artery territory. It is possible that increased blood flow could improve long-term outcomes in patients undergoing CABG; however, our results did not support this notion. Instead, the patients who received multiple grafts to each major diseased artery territory had a long-term survival similar to that of patients who received single grafts. Furthermore, although they had longer cardiopulmonary bypass and aortic crossclamp times, patients who received multiple grafts placed to each major diseased artery territory had a 30-day mortality and a major adverse cardiac event rate similar to those of patients who had traditional, single-graft complete revascularization.

Our findings refute the notion that using more bypass grafts improves CABG outcome, in that increased blood flow through multiple bypass grafts to each major diseased artery territory may not be needed as long as the patient has complete revascularization. One potential explanation for our findings comes from the work of Sand and colleagues[11] on myocardial collateral flow reserve in patients with stable angina waiting to undergo PCI. Sand and colleagues[11] showed that the severity of temporary regional myocardial hypoperfusion is significantly reduced by the presence of collaterals from other coronary vessels. Furthermore, Verhoye and colleagues[12] were able to illustrate in patients that most myocardial collateral flow after surgical revascularization is supplied by native circulation, meaning blood flow from other regional coronary arteries. These findings suggest that native collateral coronary circulation may be responsible for blood flow to nonbypassed targets in a coronary territory. This may be the reason why placing multiple grafts to each major diseased artery territory does not improve outcome as long as complete revascularization is achieved. On the basis of the aforementioned studies, it appears possible that if there is more than one bypassable target in the diseased circumflex territory, a single graft to a single target vessel may be able to supply adequate collateral flow to the other nonbypassed targets through the native circulation. This could be the mechanism that underlies our finding that placing multiple grafts to each major diseased artery territory does not produce better outcomes than traditional complete revascularization.

ACD

Our study is subject to the limitations inherent in a retrospective review. There was obvious selection bias in choosing which patients received more grafts. For example, technical considerations, the quality of target vessels, or both may have led the surgeons to place multiple grafts to each major diseased artery territory in a particular patient. Because of this, the two groups of patients in our study may not be completely matched in terms of severity of CAD. These influences on surgical decision-making may not have been noted consistently in the operative report; we therefore could not compensate for them in our data analyses. The results of this study serve as hypothesis-generating information for future prospective randomized trials to determine definitively whether placing multiple grafts to each major diseased artery territory improves long-term survival. Additionally, because the patient population at MEDVAMC is limited to veterans, nearly all our patients were men. Consequently, we cannot generalize our results to female patients. Furthermore, even though our study did not show a long-term survival difference between the two groups of patients, we may be committing a type II statistical error. With a power of 80% and α of .05, our study with 1129 patients was designed to detect a long-term survival difference of at least 8%. Thus a survival difference smaller than 8% could have gone undetected in our cohort of patients; more patients, a longer follow-up period, or both would have been needed to detect such an effect.

The goal of our research group is to improve outcomes in patients undergoing CABG. Our findings in this study represent pilot data for future prospective, randomized studies designed to ascertain further whether the construction of multiple grafts to each major diseased artery territory improves outcomes for patients undergoing CABG.

In summary, we found that patients who received multiple grafts to each major diseased artery territory had similar early outcomes to those who received single grafts. Furthermore, constructing multiple grafts to each major diseased artery territory significantly increased operative times and did not improve long-term survival. As long as patients receive traditional complete revascularization, the longer cardiopulmonary bypass and myocardial ischemic times incurred during construction of more grafts may not be justifiable according to our findings in this study.

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