SURGERY FOR ACQUIRED CARDIOVASCULAR DISEASE

BILATERAL SKELETONIZED INTERNAL THORACIC ARTERY GRAFTS IN PATIENTS WITH DIABETES MELLITUS

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Objective: Increased risk of deep sternal infections has prohibited routine bilateral internal thoracic artery grafting in diabetic patients. The technique for harvesting the skeletonized internal thoracic artery provides the potential to minimize this risk. The purpose of this study was to compare the outcome of bypass grafting with bilateral skeletonized internal thoracic arteries in diabetic and nondiabetic patients.

Methods: From May 1996 to April 1998, 231 consecutive diabetic and 534 nondiabetic patients underwent bilateral skeletonized internal thoracic artery grafting. Mean age was 66 years. Compared with the nondiabetic group, the diabetic group comprised more women (29% vs 18%, $P = .001$), had a greater prevalence of hypertension (53% vs 44%, $P = .019$) and congestive heart failure (20% vs 14%, $P = .016$), but a lower prevalence of preoperative acute myocardial infarction (26% vs 34%, $P = .027$).

Results: Operative mortality of diabetic patients was comparable with that of nondiabetic patients (3% vs 2.6%). The two groups also had similar occurrences of deep sternal infection (2.6% vs 1.7%, respectively, $P = .40$). Deep sternal infection was significantly more prevalent in obese, diabetic women (3/211 = 1.4%, $P < .0001$) (odds ratio 11.1, confidence interval 2.1-59.4). Diabetic patients also had a higher incidence of stroke (3.5% vs 0.9%, $P = .014$). Three-year actuarial survival of diabetic patients was lower (91.3% vs 94.7%, $P = .083$).

Conclusions: Bilateral skeletonized internal thoracic artery grafting is a good surgical revascularization option in diabetic patients. Operative mortality and prevalence of sternal infection are comparable with those of nondiabetic patients. However, the risk of sternal infection in obese diabetic women is high, and for them we advocate the use of a single artery instead of bilateral internal thoracic arteries. (J Thorac Cardiovasc Surg 2001;121:668-74)

A growing number of diabetic patients with multivessel coronary artery disease have recently been referred for coronary artery bypass grafting (CABG) because of an unfavorable outcome of percutaneous transluminal coronary angioplasty.^{1,2} Angioplasty in diabetic patients is associated with increased rates of

restenosis and reinterventions¹⁻⁴ and a significantly lower 5-year survival compared with CABG.^{1,2}

The improved survival of diabetic patients who underwent CABG is limited to those who received at least one internal thoracic artery (ITA) graft.^{1,5} The superior patency rate of the ITA has led many surgeons to use both ITAs for myocardial revascularization in an attempt to avoid late saphenous vein closure and postoperative return of angina. Several important studies that appeared during the past few years reported survival benefit after bilateral ITA (BITA) compared with single ITA grafting.⁶⁻¹⁰ However, extensive arterial grafting with BITAs was confined mostly to nondiabet-

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Table I. Preoperative and operative characteristics: Diabetic versus nondiabetic patients

Factor	Diabetic (n = 231)	Nondiabetic (n = 534)	P value*
Age $\geq$ 70 y	72 (31.1%)	183 (34%)	.45
Female sex	68 (29.4%)	99 (18%)	.001
Left main stenosis	56 (24.2%)	134 (25%)	.40
Acute MI > 1 wk	60 (25.9%)	182 (34%)	.03
Old MI	93 (40.2%)	188 (35%)	.19
Complicated PTCA	19 (8.2%)	61 (11%)	.20
EF $\leq$ 35%	46 (19.9%)	95 (18%)	.48
Congestive heart failure	47 (20.3%)	72 (14%)	.02
Preoperative IABP	3 (1.29%)	20 (4%)	.10
Hypertension	123 (53.2%)	235 (44%)	.02
PVD	9 (5.89%)	25 (5%)	.71
Chronic renal failure	19 (8.2%)	46 (9%)	1.00
Severe COPD	26 (11.2%)	48 (9%)	.35
Emergency surgery	21 (9.0%)	55 (10%)	.69
Repeat CABG	8 (3.4%)	14 (3%)	.49
Surgical technique (composite)	159 (68.8%)	319 (60%)	.02
Surgical technique (cross)	56 (24.2%)	169 (32%)	.02
Use of GEA	45 (19.4%)	131 (24%)	.25
Use of SVG	26 (11.2%)	64 (12%)	.90
Bypass time (min)	79 $\pm$ 37	83 $\pm$ 41	.26
Crossclamp time (min)	65 $\pm$ 28	68 $\pm$ 29	.17

MI, Myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; EF, ejection fraction; IABP, intra-aortic balloon pump; PVD, pulmonary vascular disease; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; GEA, gastroepiploic artery; SVG, saphenous vein graft.

*Fisher exact test.

ic patients because of the increased risk of deep sternal wound infection that was documented in patients who underwent surgical procedures with BITA grafting.^{11,12}

To decrease the risk of sternal infection associated with BITA harvesting, we adopted the technique of a skeletonizing dissection.¹³⁻¹⁵ The skeletonized artery is isolated gently with scissors and silver clips, without the use of cauterization. The advantage of using the ITA as a skeletonized artery is the preservation of collateral blood supply to the sternum, enabling more rapid healing and decreasing the risk of infection.¹⁶ Bilateral skeletonized ITA grafting is the preferred method for myocardial revascularization in our service. This procedure is routinely performed in most of the patients referred for CABG, including elderly, obese, and diabetic patients.

As of May 1996, 765 consecutive patients had undergone arterial revascularization with skeletonized BITA grafts, including 231 (30%) diabetic patients. The purpose of this study was to evaluate the impact of diabetes mellitus on early and 3-year outcome of this subgroup by comparing it with the group of nondiabetic patients with skeletonized BITAs.

Patients and methods

Between May 1996 and April 1998, 231 consecutive diabetic patients and 534 nondiabetic patients underwent CABG with BITA grafts at the Tel-Aviv Sourasky Medical Center. Preoperative and operative characteristic of both diabetic and

nondiabetic patients are listed in Table I. Female sex, congestive heart failure (CHF), and hypertension were more prevalent in the diabetic group than in the nondiabetic group. However, a larger number of nondiabetic patients had acute myocardial infarction (MI) preoperatively.

The ITAs were dissected as skeletonized arteries¹³ before heparin administration to decrease the risk of damage and hematoma formation in the region of the side branches during dissection. The operations were performed with cardiopulmonary bypass. The myocardial preservation technique involved intermittent infusion of warm cardioplegic solution (30°C-32°C).¹⁷ In 45 diabetic patients (19%) and in 131 nondiabetic patients (24.5%), the right gastroepiploic artery was used as a third arterial conduit to bypass the posterior descending branch of the right coronary artery. A composite graft was prepared before connection to cardiopulmonary bypass in 478 patients (62%) (Table I). Most of the composite grafts included end-to-side anastomosis of a free right ITA on an in situ left ITA. When the proximal part of the left ITA was damaged, or when its spontaneous free flow was not sufficient, a free left ITA was anastomosed end to side to an in situ right ITA. A third variation was the small Y-graft, wherein a small distal section of an ITA was anastomosed end to side to a more proximal part of the same artery.

When no graft to the posterior wall of the heart was necessary (the circumflex region), the left ITA was grafted to the left anterior descending coronary artery and the right ITA to the right coronary artery or to its posterior descending branch. In most cases it is impossible to reach this branch of the right coronary artery when using the regular technique of isolating the pedicled ITA. The skeletonized right ITA, how-

Table II. Outcome events: Diabetic versus nondiabetic patients

	Total group (n = 765)	Diabetic (n = 231)	Nondiabetic (n = 534)	P value*
Operative mortality	21 (2.7%)	7 (3.0%)	14 (2.6%)	.80
Three-year survival	93% $\pm$ 2%	91.3% $\pm$ 2%	94.7% $\pm$ 1%	.08†
CVA	13 (1.7%)	8 (3.5%)	5 (0.9%)	.014
Perioperative MI	9 (1.2%)	0 (0%)	9 (1.7%)	.06
Sternal infection	15 (1.9%)	6 (2.6%)	9 (1.7%)	.40
Return of angina	15 (1.9%)	4 (1.7%)	11 (2.0%)	1.00

CVA, Cerebrovascular accident; MI, myocardial infarction.

*Fisher exact test.

†Log rank test.

ever, is longer and therefore can usually reach the better quality distal posterior descending artery.

To decrease the risk of spasm of the arterial grafts, we treated all patients with high-dose intravenous infusion of isosorbide dinitrate (Isoket) (4-20 mg/h) during the first postoperative 24 to 48 hours. Systolic blood pressure was maintained above 100 to 120 mm Hg. From the second postoperative day, the patients were treated with calcium channel blockers (diltiazem 90-180 mg/day orally) for at least 3 months.

Statistical analysis. Data are expressed as mean $\pm$ SD or proportions as appropriate. The χ^2 test was used for late events and the Fisher exact test for the remaining discrete variables. A 2-sample *t* test was used to compare discrete and continuous variables. Multivariable logistic regression analysis was used to predict unfavorable outcome events by various risk factors. Odds ratio (OR) and 95% confidence intervals (CI) are given. Postoperative survival is expressed by the Kaplan-Meier method and survival was compared by the log rank test. The Cox proportional hazard model was used to evaluate risk factors for overall mortality in diabetic patients. All analyses were performed by SPSS 9.0 software (SPSS, Inc, Chicago, Ill).

Results

The 765 patients with skeletonized BITA grafts received 2 to 5 (mean 3.2) grafts per patient. The average cardiopulmonary bypass time was 79 ± 37 minutes, and aortic crossclamping time was 65 ± 28 minutes. Operative mortality of the 231 diabetic patients was 3% (7 patients) (Table II), which was not significantly different from the mortality of the 534 nondiabetic patients with skeletonized BITA grafts (2.6%, 14 patients) (Table II). (Operative mortality was defined as death occurring during hospitalization for the operation, no matter how long after the original operation the death occurred, and/or any death within 30 days in patients who were discharged from the hospital.) However, diabetic patients had higher rates of perioperative stroke (cerebrovascular accident [CVA] resulting in permanent neurologic deficits and computed tomographic evidence of cerebral infarction) (3.5% vs 0.9%, $P < .05$).

To determine whether the increased incidence of neurologic complications was a consequence of the fact that hypertension, CHF, and female sex were more prevalent in this group, we performed a multivariate analysis with diabetes as a dependent variable. We first included the variables to be controlled as covariates (hypertension, sex, CHF, and acute MI) and then CVA. The logistic regression model showed that even after controlling for these variables, the higher incidence of CVA in diabetic patients was still statistically significant, suggesting that the tendency toward CVA is more pronounced in diabetic patients. This increased risk of stroke in diabetic patients is not a consequence of other preoperative risk factors. Moreover, after analyzing the variables predictive of CVA, we found that diabetes was the only variable that was predictive of CVA even in the univariate analysis.

There were no perioperative MIs (usually defined by the appearance of new Q waves in the electrocardiogram associated with serum levels of creatine kinase MB fraction > 50 mU/mL) among the diabetic patients (1.7% perioperative MIs in nondiabetic patients, $P < .05$), and the rates of deep sternal wound infection were similar in the two groups (2.6% vs 1.7%, respectively).

The univariate analysis performed in the diabetic group revealed female sex and obesity to be significant risk factors for deep sternal infection; however, only the combination of obesity and female sex was an independent risk factor for this complication (OR 11.1, CI 2.1-59.4) (Table III).

Postoperative follow-up from 1 to 3 years was available in 730 of 737 surviving patients (97%). There were 32 (4.1%) late deaths, 8 of which were unrelated to the operation. The 1- and 3-year actuarial survivals (Kaplan-Meier) of the diabetic patients were lower than those of nondiabetic patients (94.3% and 91.3% vs 96.2% and 94.7%, respectively). However, the difference did not reach statistical significance ($P = .083$).

Table III. Characteristics of diabetic patients and sternal wound infection

Characteristics	Prevalence (n= 231)		Infection with characteristic		Infection without characteristic		P value
	No.	%	No.	%	No.	%	
Age ≥ 70 y	73	31.6	1	1.3	5	3.1	
Female sex	68	29.4	4	5.8	2	1.2	.043
Obesity	48	20.7	4	8.3	2	1.1	.033
Female obesity	20	8.6	3	15.0	3	1.4	.001
IDDM	14	6.0	1	7.1	5	2.3	
Chronic renal failure	17	7.35	1	5.8	5	2.3	
Severe COPD	26	11.25	2	7.6	4	1.9	
Emergency surgery	21	9.0	1	4.7	5	2.3	
Repeat CABG	7	3.0	0	0	6	2.6	

IDDM, Insulin-dependent diabetes mellitus; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting.

Table IV. Overall (early and late) mortality of diabetic patients (n = 21)

Factor	Mortality with factor		Mortality without factor		P (Cox model)	HR	CI
	No.	%	No.	%			
Age ≥ 70 y	12	16.4	9	5.9	.26	3.6	1.3-10.1
EF ≤ 35%	10	21.7	11	5.9	.007	5	1.8-13.7
CHF	10	20.8	11	6.0	.0035	3.1	1.9-8.7
Emergency surgery	6	28.5	15	7.1	.007	5	1.4-14

HR, Hazard ratio; CI, 95% confidence interval; EF, ejection fraction; CHF, congestive heart failure.

None of the preoperative characteristics of the diabetic patients was found to be a significant predictor of early mortality; however, univariate analysis revealed age over 70 years, left ventricular ejection fraction less than 35%, CHF, and emergency operation to be predictors of overall (ie, combined early and late) mortality. Older age, emergency operation, and ejection fraction less than 35% were also found to be independent predictors in the multivariate analysis (Table IV).

Discussion

Unlike pedicled ITA harvesting, skeletonizing dissection of the ITA leaves the vein, muscle, and accompanying endothoracic tissue in place. Besides preserving collateral sternal blood supply and minimizing the risk of deep sternal infection, the advantage here is that the dissected artery is longer, and its spontaneous blood flow is greater than that of the pedicled ITA,^{14,18} allowing the use of both ITAs as grafts to almost all necessary coronary vessels. No additional vein graft is required in most cases.¹⁹

The findings in our current report do not directly prove that sternal collateral blood supply is improved with skeletonized ITA dissection. However, they do strengthen the basic assumption concerning this har-

vesting technique, that it causes less damage to sternal blood flow^{15,20,21} and therefore enables the use of BITA grafts in diabetic patients. Diabetes mellitus alone was found not to be a significant risk factor for early mortality or deep sternal infection when BITAs are harvested as skeletonized arteries. The current study also delineated a subgroup of diabetic patients with increased risk of deep sternal wound infection—diabetic obese women. The combination of diabetes, obesity, and female sex was found to be associated with a 10-fold rate of deep sternal infection (15% vs 1.4% in diabetic patients without this combination of risk factors). Previous reports have shown obesity to be an independent risk factor for deep sternal infection and sternal dehiscence.^{11,22,23} A study by Loop and associates¹¹ of 6504 consecutive patients having CABG identified obesity (OR 2.9) as the most important risk factor for sternal wound complications. Other risk factors for this complication included BITA grafting, diabetes mellitus, and old age. In another recently published study of 11,101 CABG patients by Birkmeyer and coworkers,²³ the risk of sternal wound infection was more than twice as high among the obese and nearly three times higher among the severely obese CABG patients. In view of this unacceptably high risk of ster-

Fig 1. Survival curves (Kaplan-Meier) of the diabetic and nondiabetic study patients.

nal infection, we do not advocate the use of BITA grafts in obese diabetic women, for whom we prefer to use single ITA and saphenous vein grafts.

We also found a 4-fold increase in the rate of postoperative stroke in diabetic patients compared with nondiabetic patients (3.5% vs 0.9%). Moreover, the univariate analysis revealed diabetes mellitus to be the only significant predictor of postoperative stroke in the cohort of 765 patients who had CABG with skeletonized BITAs. Similar findings were described in diabetic patients from western Sweden, who displayed a higher incidence of perioperative and postoperative neurologic complications when compared with nondiabetic patients.²⁴ In another report from Emory University in Atlanta, stroke was significantly more prevalent in patients with diabetes than in those without diabetes (2.9% vs 1.4%, respectively, $P < .05$).²⁵

A recently published multicenter prospective study on 2108 patients by Roach and colleagues²⁶ reported an incidence of 6.1% for adverse cerebral outcome and of 3.1% for strokes (fatal and nonfatal) after CABG. The incidence of strokes was 5 times higher in patients with intraoperatively palpable atherosclerotic plaque in the proximal aorta. In this study, diabetes was defined as a significant risk factor for stroke (OR 2.46). Despite the relatively older age of our patients (mean 66.3 years, 33% older than 70 years), the rate of postoperative stroke was slightly lower than that in the report by Roach and associates²⁶ (1.7% vs 3.1%). This may be explained by the fact that complete arterial revascularization was achieved without the use of vein grafts in 89% of our patients. Complete arterial revascularization permits the limitation of aortic manipulations to the necessary procedures alone, that is, aortic cannulation, insertion of cardioplegia needles, and crossclamping

of the aorta. In this technique, the ITAs are used as the sole source of blood supply for CABG to eliminate manipulation of the aorta when there is atheromatous plaque (the “no-touch” technique).²⁷

The diffuse and advanced nature of the atherosclerotic plaques in the aorta and brain vessels of diabetic patients is probably the most likely explanation for the higher incidence of stroke.^{28,29} Another possible explanation is the elevated level of β -thromboglobulin and circulating platelet aggregates in the blood of diabetic patients, which may reflect platelet activation and may cause postoperative microemboli.³⁰ Finger palpation of the ascending aorta may underestimate the frequency and severity of atherosclerotic plaques involving this part of the aorta. Epiaortic or transesophageal echocardiography might improve intraoperative detection of pathologic aortic plaques and thus reduce the rate of postoperative strokes.

The midterm results of this study include up to 3 years of follow-up. Late and overall mortality rates of patients with diabetes were higher than those of patients without diabetes (6% and 9% vs 2.8% and 5.4%). The 3-year actuarial survival of nondiabetic patients was better, but the difference between survivals was not significant, probably because of the relatively short period of follow-up. The adverse effect of diabetes mellitus on late survival was described by Morris,³¹ Lawrie,³² Thourani,²⁵ and their colleagues.

Our report suggests that diabetes may be an important risk factor for late mortality at a longer follow-up period, even in patients undergoing arterial myocardial revascularization with BITAs. We found emergency operation, older age, and severe left ventricular dysfunction to be predictors of late mortality in diabetic patients.

In summary, the use of BITA grafting is an appropriate surgical revascularization technique for diabetic patients. It provides multiple arterial grafting with the best conduits (ITAs) and at the same time is associated with a relatively low risk of deep sternal infections. The prevalences of early mortality and deep sternal infection in diabetic patients in this study are similar to those of nondiabetic patients. The occurrence of perioperative MI in diabetic patients was low. However, our study showed that diabetic patients have an increased risk of stroke, which is probably related to the diffuse character of their atherosclerotic disease. The 3-year cumulative survival was favorable, albeit not as good as in the nondiabetic patients. Long-term follow-up of randomized studies comparing this surgical technique to the more conventional techniques (left ITA plus saphenous vein graft) is needed.

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