

Off-Pump Coronary Revascularization of the Circumflex System: Comparison between Sequential and Nonsequential Arterial Grafts

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ABSTRACT

Background: Sequential grafting increases the availability of arterial grafts. This study aims to determine the safety and efficacy of sequential grafting of the circumflex coronary distribution performed off-pump.

Methods: Between 2000 and 2003, 136 patients undergoing off-pump sequential arterial grafting of the circumflex territory were compared to 278 patients who received nonsequential grafts to the same area.

Results: The grafts/patient ratio was higher in the sequential than the nonsequential group ($3.2 \pm .4$ and $2.3 \pm .2$, respectively, $P < .0001$). Radial artery conduits and T-grafts were used more often in the sequential group; conversely, bilateral internal thoracic artery configurations were more frequent in the nonsequential groups ($P < .0001$). There were 1.2 sequential anastomoses per patient. Early mortality (2.2% versus 2.5%), myocardial infarction (2.2% versus 1.1%) and stroke (.7% versus none) rates were comparable. Use of sequentials or other operative confounders had no independent effect on the occurrence of early adverse events (stepwise logistic regression). At 3.5 years, survival was 95.9% and 84.2% in the sequential and nonsequential groups, respectively ($P = .231$, log-rank). Despite comparable incidence of major adverse cardiac events (MACE) (6.6% versus 8.6%, $P = .470$) and similar 3.5-year freedom from MACE (88.7% for both groups, $P = .682$), Cox regression analysis identified sequential grafting as an independent predictor of MACE ($P < .0001$, HR 19.9), increasing this risk by 20-fold.

Conclusions: Off-pump sequential grafting of the circumflex system may be safely performed. The use of sequentials, however, had an independent effect on increased mid-term MACE. The distribution of events suggests culpability of surgical factors and may reflect a learning curve.

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INTRODUCTION

Sequential grafting increases the availability of arterial conduits [Dion 2000]. The feasibility of on-pump application of this technique is reflected by an overall 7.5-year patency of 96% and a 94% patency for circumflex (Cx) territory sequential internal thoracic artery (ITA) anastomoses [Dion 2000].

Advances in retractor-stabilizer devices allowing access to all coronary segments have led to increased use in off-pump coronary artery bypass (OPCAB). Correspondingly, the resurgent interest in strategies reducing the extent of surgical aortic manipulation [Calafiore 2002, Lev-Ran 2004] and the motivation to improve long-term outcomes [Buxton 1998, Taggart 2001] has resulted in growing demand for arterial conduits. By avoiding the need to attach grafts to the aorta, composite or in situ arterial configurations during OPCAB enable clampless no-touch aorta revascularization. These techniques are particularly attractive in face of the older and sicker patients currently referred to surgery [Ferguson 2002] who are prone to atherosclerotic aortic disease and subsequent atheroembolic-related stroke [Wareing 1992]. The choice of arterial conduits appears essential in light of a recent report demonstrating that composite attachment of saphenous vein compromises the distal ITA segment, thus precluding the use of ITA-vein composite grafts [Gaudino 2004].

To date, there are no published studies that have focused on sequential Cx grafting during OPCAB and the small datasets of patients that have been thus far reported do not offer a clear mandate for routine use of this strategy.

The aim of this study was to assess the safety and mid-term efficacy of off-pump sequential arterial grafting of the Cx territory.

MATERIALS AND METHODS

Study Design

A total of 770 consecutive patients underwent multivessel OPCAB between September 2000 and September 2003. The data of 414 patients among them who underwent total arterial revascularization with grafting of the Cx territory were analyzed. Specifically, the 136 patients in whom sequential Cx grafting was performed (sequential group) were compared to

278 patients in whom the same area was grafted by nonsequential arterial grafts (nonsequential group).

This study cohort constituted 41% of all (ie, 1000) off-pump procedures performed during the designated period. The left Cx marginal arteries were grafted in all of them. Excluded were patients who underwent anterior wall left anterior descending (LAD)-diagonal sequential grafting and those who received vein grafts. In addition, neurologically symptomatic patients or asymptomatic patients ≥ 65 years of age were screened preoperatively by carotid Doppler assays: those requiring carotid endarterectomy (ie, symptomatic with unilateral stenosis $>70\%$ or asymptomatic with severe bilateral stenosis) were also excluded.

Surgical Technique and Postoperative Management

Operations were performed through a mid-line sternotomy. Anticoagulation was achieved using 2 mg/kg heparin and the activated clotting time was maintained above 300 seconds. The heart was stabilized using a suction tissue stabilization system (Octopus, Medtronic Inc, Minneapolis, MN). A deep pericardial retraction suture was placed at the posterior fibrous pericardium medial to the proximal part of the inferior vena cava to help manipulate and rotate the heart to vertical and lateral positions. A right-sided pericardial incision directed toward the inferior vena was selectively performed to facilitate venous return. Vessel occlusion was achieved by external encircling silicone rubber bands. Intracoronary shunts were used occasionally.

Conduits used for left-sided revascularization were the left and right ITAs and the radial artery (RA). The two configurations that were employed were an in situ bilateral ITA or T-graft. In situ grafting included in situ anteaortic crossover right ITA directed to the LAD and an in situ left ITA for grafting the Cx marginals [Lev-Ran 2002]. T-grafts were composed of a right ITA or an RA attached to an in situ left ITA. All ITAs were mobilized as skeletonized vessels [Lev-Ran 2002]. Relative contraindications for bilateral ITA grafting included female gender with a body mass index of ≥ 30 kg/m², patients with chronic lung disease, and insulin-treated diabetic patients [Lev-Ran 2002]. Bilateral ITA grafting was not carried out only when there was a high risk for sternal infection (according to the above-mentioned criteria), and irrespective of the patient's cardiac or other risk factors. A target coronary stenosis of $\geq 70\%$ was a prerequisite for using an RA [Maniar 2002]. Dissection of the RA was facilitated by an ultrasonic scalpel (Harmonic Scalpel, Ethicon Endosurgery, Cincinnati, OH). There were no contraindications for RA use, unless a preexisting disease was detected during harvesting and the vessel was defined as being inadequate for grafting. The choice of conduits and grafting configurations was determined by technical considerations, particularly those related to the conduit's availability and length.

Right-sided revascularization was performed with ITA, RA or right gastroepiploic artery (RGEA) grafts. The use of RGEA required critical target vessel stenosis [Suma 2000]. T-anastomoses were constructed prior to the distal coronary anastomoses, and anterior wall revascularization was routinely performed first in the sequence of grafting in both groups.

Sequential anastomoses were constructed as diamond-shaped and performed prior to the terminal ones to provide a functional graft with the completion of each anastomosis.

Postoperatively, all patients received intravenously administered isosorbide dinitrate (4-20 mg/h) for two days. Oral calcium blockers (Dilatam, Teva, Petah-Tikva, Israel) were given to patients who received RA or RGEA conduits and the medication was continued for 6 months postoperatively. All patients received aspirin 250 mg per day (recommended for indefinite use) and Clopidogrel 75 mg per day (Plavix, Sanofi Winthrop, France) for 6 weeks.

Postoperative angiography was performed selectively, that is, only in symptomatic patients (return of angina or undetermined chest pain) or in those with a positive radionuclear scan.

Definition of Terms and Data Collection

Patients' data were collected and analyzed according to the STS National Cardiac Surgery database guidelines and definitions (<http://www.ctsnet.org/doc/4314>). Chronic renal dysfunction was defined as preoperative serum creatinine of 2 mg/dL or more. Early mortality was defined as death occurring within 30 days of the operation. The endpoint of early events was defined as the occurrence of one of the following: early mortality, perioperative myocardial infarction (MI), perioperative stroke or deep sternal infection. Causes of late death were classified as either cardiac or noncardiac. Late cardiac mortality was defined as death occurring in relation to MI, cardiac arrhythmia, out-of-hospital sudden death or deteriorating congestive heart failure. An undetermined cause of death was regarded as being cardiac. Major adverse cardiac events (MACE) were defined as the occurrence of one of the following: nonfatal MI, need for repeat revascularization or cardiac mortality.

Follow-up information was obtained by a telephone questionnaire and the national registry database.

Data Analysis

Data are expressed as mean \pm standard deviation. The χ^2 test was used to compare categorical variables. Student's *t*-test and the Mann-Whitney test were used for the comparison of continuous variables. Actuarial survival curves were obtained with the Kaplan-Meier method. Statistical significance was calculated with the log-rank test. Stepwise logistic regression was used to evaluate the effect of preoperative and operative confounding factors on the occurrence of early mortality and early major events. Cox analysis was used to evaluate the effect of these variables on mid-term mortality and the occurrence of MACE. Results of stepwise logistic regression were expressed as odds ratio (OR) with associated 95% confidence interval limits (CL) and *P*-values. Results of Cox regression analysis were expressed as hazard ratio (HR) with associated 95% CL and *P*-values. All analyses were performed by SPSS 12 software (SPSS Inc, Chicago, IL).

RESULTS

Preoperative parameters were assessed for their effect on survival and complications by univariate analysis. Baseline characteristics were comparable between the two groups

Table 1. Preoperative Characteristics*

Variable	Sequential group n = 136	Nonsequential group n = 278	P
Age, y			
mean	69.7 ± 9.8	67.8 ± 11.3	.086
range	44-86	41-90	
Age >75 y	43 (31.6)	75 (27.1)	0.337
Age >80 y	16 (11.8)	30 (10.8)	0.777
Female gender	38 (27.9)	72 (25.9)	0.659
Hypertension	97 (71.3)	177 (63.7)	0.122
Diabetes mellitus	61 (44.9)	99 (35.7)	0.074
Peripheral vascular disease	26 (19.3)	50 (18.1)	0.767
Chronic renal dysfunction	7 (5.1)	16 (5.8)	0.800
Chronic lung disease	12 (8.8)	28 (10.1)	0.686
Prior cerebrovascular disease	12 (8.8)	19 (10.4)	0.607
Acute MI (<1 wk)	16 (11.8)	30 (10.8)	0.767
Congestive heart failure	22 (16.2)	45 (16.2)	0.998
Left main stenosis (>50%)	33 (24.4)	84 (30.5)	0.199
3-vessel disease	115 (84.5)	215 (77)	0.086
Ejection fraction ≤35%	10 (7.5)	22 (8.0)	0.857
Emergency operation	8 (5.9)	21 (7.6)	0.531
Preoperative IABP	8 (5.9)	18 (6.5)	0.815
Euroscore-predicted mortality	5.3%	4.9%	0.670

*Variables are expressed as n (%). MI indicates myocardial infarction; IABP, intra-aortic balloon pump.

(Table 1). Operative data are listed in Tables 2 and 3: both groups had the same level of surgical risk. Sequential grafting was performed in 33% of the patients. The respective grafts/patient ratio was $3.2 \pm .4$ and $2.3 \pm .2$ in the sequential and nonsequential groups ($P < .0001$) (Table 2). The 1.2 sequential anastomoses per patient that were performed were distributed on either the RA (n = 101) or the ITA (n = 61) conduits. The type of conduit, graft configuration and the

corresponding target coronary arteries are listed in Tables 2 and 3. The distribution of Cx branches (ie, intermediate branch, 1st marginal, 2nd marginal, 3rd marginal and posterolateral branch) was comparable between the groups. Radial arteries were used more often in the sequential group (Tables 2 and 3). Multiple sequential anastomoses were performed in 29 (21.3%) patients of the sequential group. Avoidance of aortic manipulation (“no-touch aorta”) was achieved

Table 2. Operative Data*

Variable	Sequential group n = 136 (%)	Nonsequential group n = 278 (%)	P
Grafts/patient ratio			
mean	3.2 ± 0.4	2.3 ± 0.2	<0.0001
range	2-4	2-4	
Use of LITA	135 (99.3)	275 (99.3)	0.988
Use of RITA	50 (36.8)	189 (68.2)	<0.0001
Use of BITA	45 (33.1)	189 (68.5)	<0.0001
Use of radial artery	90 (66.2)	78 (28.4)	<0.0001
Use of RGEA	2 (1.5)	27 (9.7)	0.002
T-grafts	105 (77.2)	98 (35.3)	<0.0001
No-touch aorta	136 (100)	267 (96)	
No. of sequentials > 1	26 (19.1)	—	
Patients receiving sequential anastomoses on LITA	22 (16.1)	—	
Patients receiving sequential anastomoses on RITA	27 (19.8)	—	
Patients receiving sequential anastomoses on radial artery	87 (63.9)	—	

*Variables are expressed as n (%). LITA indicates left internal thoracic artery; RITA, right internal thoracic artery; BITA, bilateral internal thoracic artery; RGEA, right gastroepiploic artery.

Table 3. Conduits Used and the Corresponding Target Coronary Vessels*

Variable	LITA	RITA	RA	RGEA
LAD	261	153	—	—
Diagonal	23	—	18	—
Cx marginal	147	61	120	—
RCA	—	9	—	—
PDA	4	11	89	25
No. of sequentials	26	35	101	—

*Variables are expressed as n. LITA indicates left internal thoracic artery; RITA, right internal thoracic artery; RA, radial artery; RGEA, right gastroepiploic artery; LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery; PDA, posterior descending artery.

in 100% and 96% of the sequential and nonsequential groups, respectively.

Operative Mortality and Morbidity

Data on operative and morbidity are listed in Table 4. The logistic Euroscore-predicted-mortality was 5.3% (CL, .034-.071) for the sequential group and 4.9% (CL, .041-.057) for the nonsequential group ($P = .670$); standard Euroscore: 4.2% and 3.9%, respectively ($P = .358$). There was no difference between the groups in the incidence of 30-day mortality, perioperative MI, major neurological events or sternal complications (Table 4).

Follow-up Status

Follow-up ranged from 6 to 41 months (median, 22 months) and was ascertained for 97% of the patients. Mid-term results are presented in Table 4. Coronary angiography was performed in 28 patients (28/414, 6.8%) between 1 and 39 months postoperatively (median, 13 months): the patency rate

was 91% for the sequential patients ($n = 7$) and 94% for the nonsequential patients ($n = 21$). Three (3/136, 2.2%) coronary angioplasties were performed in the sequential group. Repeat revascularization was performed in 12 (12/278, 4.3%) patients in the nonsequential group: 10 angioplasties and two reoperations. This difference in reintervention rate between the two groups was not statistically significant (Table 4).

Survival outcomes were assessed by the Kaplan–Meier model. The 1- and 3.5-year survival was 97.4% and 95.9% for the sequential group and 98.3% and 84.2% for the nonsequential group, ($P = .231$, log-rank). One-year freedom from cardiac mortality was 98.1% and remained the same at 3.5 years in the sequential group (all cardiac-related deaths occurred within the first year). It was 99.5% at one year and 97.2% at 3.5 years for the nonsequential group ($P = .879$, log-rank). One- and 3.5-year freedom from MACE was 97.4% and 88.7% in the sequential group (50% of all events occurred during the first year) and 98.2% and 88.7% in the nonsequential group (25% of all events occurred during the first year) ($P = .682$, log-rank).

Analysis of Morbidity and Mid-Term Adverse Outcome

Stepwise logistic regression was used to assess the effect of confounding factors on early mortality and early major events (Table 5). Included in the analysis were recognized independent risk factors of adverse outcome (age, gender diabetes, hypertension, peripheral vascular disease, chronic renal failure, chronic lung disease, history of cerebrovascular disease, ejection fraction <35%, left main coronary artery disease and emergent operation) and confounding operative variables (number of grafts and use of sequential, bilateral ITA, RA, RGEA and composite grafts).

After adjustment for all explanatory variables, emergent operation was identified as an independent predictor of early mortality (OR 6.8) (Table 5) and peripheral vascular disease (OR 3.9), history of cerebrovascular disease (OR 4.7) and

Table 4. Early and Mid-term Results*

Variable	Sequential group n = 136	Non sequential group n = 278	Total n = 414	P
Length of hospital stay, d				
mean	5.7 ± 2.6	5.6 ± 2.9	5.6 ± 2.8	0.980
range	4-20	4-23		
30-day mortality	3 (2.2)	7 (2.5)	10 (2.4)	0.846
Myocardial infarction	3 (2.2)	3 (1.1)	6 (1.5)	0.370
Perioperative stroke	1 (0.7)	—	1 (0.2)	0.153
Re-exploration d/t bleeding	1 (0.7)	4 (1.4)	5 (1.2)	0.536
Deep sternal infection	—	5 (1.8)	5 (1.2)	0.117
Recurrent angina	3 (2.2)	15 (5.4)	18 (4.3)	0.134
Repeat revascularization	3 (2.2)	12 (4.3)	15 (3.6)	0.280
Late non-fatal MI	4 (2.9)	6 (2.1)	10 (2.4)	0.626
Late mortality	4 (3)	18 (6.7)	22 (5.3)	0.126
Late cardiac mortality	2 (1.5)	6 (2.3)	8 (1.9)	0.600
MACE†	9 (6.6)	24 (8.6)	33 (7.9)	0.470

*Variables are expressed as n (%). MI indicates myocardial infarction; MACE, major adverse cardiac events.

†The occurrence of one or more of the following: late non-fatal MI, re-intervention or cardiac-related mortality.

Table 5. Stepwise Logistic Regression: Independent Risk Factors for Early Mortality and Early Major Events*†

Variable	Early mortality			Early major events		
	OR	95% CL	P	OR	95% CL	P
PVD				3.9	1.44-10.8	0.007
Cerebrovascular disease				4.7	1.49-14.7	0.008
Emergent operation	6.8	1.65-28.2	0.008	4.2	1.04-17.6	0.043
Use of sequentials	0.9	0.23-37.2	0.922	1.1	0.40-3.32	0.776

*Significance was set at $P < 0.05$. The occurrence of one or more of the following: early mortality, perioperative MI, stroke or deep sternal infection. OR indicates odds ratio; CL, confidence limit; PVD, peripheral vascular disease.

emergent operation (OR 4.2) as independent predictors of early major events (Table 5). The use of sequential grafts was not a multivariate correlate of early mortality ($P = .922$) or early major events ($P = .776$) (Table 5). Similarly, the number of grafts performed and the use of bilateral ITA, RA, RGEA grafts or T-configurations did not have an independent effect on these endpoints.

Cox regression analysis on the same variables was performed with regard to survival (all-cause mortality) and the occurrence of MACE (Table 6). Chronic renal dysfunction (HR 6.3), history of cerebrovascular disease (HR 2.9) and ejection fraction $<35\%$ (HR 6.1) were identified as predictors of mid-term mortality (Table 6). Diabetes mellitus (HR 2.3), ejection fraction $<35\%$ (HR 5.8) and use of sequentials (OR 19.9) were risk factors for the occurrence of MACEs (Table 6).

DISCUSSION

The results of this study indicate that off-pump sequential grafting of the Cx territory using RA or ITA can be performed safely. The effect of sequential grafting on mid-term occurrence of MACE identified in multivariate analysis in this study should be further evaluated.

Both study groups had comparable preoperative profiles. The similarity in predicted risk scores, with a trend toward higher risk in the sequential group, argues against preselection of patients at lower risk to this group. The significant differences in the operative variables (Table 2) reflect distinct technical aspects of each surgical approach. Multivariate analyses were performed on early and mid-term endpoints to control for these confounding factors and avoid potential bias of these operative differences.

The OPCAB results of the current study indicate that sequential grafting of the Cx territory does not increase short-term risks. The incidence of early mortality was comparable with the nonsequential control group and both rates compared favorably with the respective calculated Euroscore-predicted mortality. These results are compatible with the reported range of early mortality for several corresponding multivessel OPCAB series [Arom 2000, Mack 2004]. After controlling for preoperative and operative confounders, sequential grafting did not emerge as a multivariate correlate of either early mortality or early major events (an endpoint defined to increase the number of events and, therefore, the statistical power of the analysis). Consistent with previous observations, emergent operation [Nilsson 2004] independently also predicted early mortality in this study, and a history of cerebrovascular [Rorich 1990] and peripheral vascular [Rorich 1990, Stamou 2001] diseases independently correlated with early major events.

An important finding here is that sequential grafting of the Cx territory emerged as a risk factor for the occurrence of MACE (Cox regression analysis), increasing the risk by 20-fold. This effect was independent of confounding factors and regardless of the fact that group dissimilarities in univariate analyses and Kaplan–Meier survival outcomes were not significant. The number of postoperative coronary angiographies conducted on our patients is too small to differentiate between surgeon-related causes and/or factors intrinsic to the technique. The distribution of cardiac-related events, however, may indicate that, unlike the nonsequential group, most events in the sequential group occurred within the first postoperative year, and this may reflect some surgery-related factors. Also, the fact that the majority of events occurred

Table 6. Cox Regression Analysis: Independent Risk Factors for Mid-term Mortality and Major Adverse Cardiac Events (MACEs)*

Variable	All-cause mid-term mortality			MACEs		
	HR	95% CL	P	HR	95% CL	P
Diabetes mellitus				2.3	1.00-5.40	0.048
Chronic renal dysfunction	6.3	2.43-16.5	<0.0001			
Cerebrovascular disease	2.9	1.06-8.17	0.037			
EF $<35\%$	6.1	2.49-15.2	<0.0001	5.8	2.25-15.1	<0.0001
Use of sequentials	0.5	0.18-1.70	0.305	19.9	4.56-86.8	<0.0001

*Significance was set at $P < 0.05$. The occurrence of one or more of the following: late non-fatal MI, re-intervention or cardiac-related mortality. HR indicates hazard ratio; CL, confidence limit; EF, ejection fraction.

among patients operated on during the first months of the study may reflect a learning curve.

The observation that RA conduits are used more often for sequential grafting and that bilateral ITAs are used for nonsequential grafting may have an impact on long-term results. Despite considerable additional ITA length conferred by skeletonized mobilization [Lev-Ran 2002], RA conduits are usually longer and may, therefore, increase surgical versatility. While it was not evident in our mid-term follow-up results, concerns have been raised regarding long-term outcome of RA grafts [Khot 2004]: improved survival has thus far been linked only to left-sided bilateral ITA revascularization [Schmidt 1997, Taggart 2001].

From a technical point of view, length assessment of intercoronary graft segments is more accurately carried out during off-pump sequential grafting on a noncollapsed heart compared to grafting on a flaccid on-pump heart in cardiac arrest. Graft tenting due to distance overestimation or segment shortage, therefore, is less likely when the technique is sequential.

Patency rates could not be extrapolated from this study due to the stringent indications for coronary angiograms. There is a paucity of data on this issue in the literature, but excellent immediate post-OPCAB patency (of 98%) and stenosis-free (96%) rates of sequential grafts were recently reported [Matsuura 2004]. The proportion of these grafts in Cx territory, however, was not specified [Matsuura 2004].

Several limitations of this study need to be addressed. There were inherent differences between the conduits and configurations of the operative techniques, although their effect was considered when carrying out the multivariate analysis. We had too few angiographic controls to identify the reason for the independent effect of sequential grafting on increased MACE.

In conclusion, our results validated the safety of off-pump sequential grafting of the Cx territory using either ITA or RA conduits. The finding by multivariate analysis that this technique has an independent effect on the occurrence of mid-term MACEs needs to be further investigated.

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