J CARDIOVASC SURG 2007;48:207-14

Determinants of late outcome after minimally invasive direct coronary artery bypass

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Aim. **Minimally invasive direct coronary artery bypass (MIDCAB) is a reliable method to revascularize the left anterior descending (LAD) coronary artery. However, a more consistent body of knowledge is needed to assess factors influencing long-term outcome. With this study, we retrospectively investigated the long-term determinants of survival and freedom from cardiac morbidity and revascularization in patients who underwent MIDCAB.**

Methods. **From 1997 to 2005, 109 patients underwent MIDCAB. Seventy-five (68.8%) presented isolated LAD disease and 34 (31.2%) multivessel disease. The first 57 patients (53.2%) in the series underwent early postoperative angiographic reinvestigation. All 109 patients were subsequently followed-up at our outpatient clinic. Follow-up (mean 50.7 months, range 3-93) was completed in 100% of cases.**

Results. **No in-hospital deaths occurred; 2 patients (1.8%) experienced perioperative myocardial infarction. At early postoperative angiographic reinvestigation, the anastomotic perfect patency rate was 54/57 (94.7%); survival was 100% and 95.8% at 1 and 5 years, respectively. Overall freedom from repeated revascularization was 95.3% and 88.3% at 1 and 5 years respectively; freedom from LAD revascularization was 95.3% and 91.6% at 1 and 5 years, respectively; cardiac event-free survival was 95.3% and 80.8% at 1 and 5 years respectively. At multivariable analysis (Cox regression), women were found to have a higher risk of repeated LAD revascularization (hazard ratio [HR] 30.24; P<0.001); female sex and left ventricular dysfunction were the only predictors affecting long-term cardiac outcome (hazard ratio 29.35; P<0.001 and 5.1; P<0.001), respectively.**

Conclusion. **A key factor in the long-term success of MIDCAB seems to be appropriate patient selection. Special attention should be reserved for female patients, as they appear to have a worse cardiac outcome and a higher probability of repeated revascularization on LAD. MIDCAB may represent a viable option for treating multivessel disease when complete revascularization is unfeasible or a hybrid procedure is envisaged.**

KEY WORDS: Minimally invasive surgical procedures - Coronary artery bypass - Treatment, outcome.

Received on September 9, 2006.
Accepted for publication on March 16, 2007.

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Minimally invasive direct coronary artery bypass (MIDCAB) has become a well established procedure for left anterior descending (LAD) coronary artery revascularization. Satisfactory early and mid-term clinical and angiographic results have been variously reported.[1-4] Quality of life after MIDCAB has also been favourably compared with conventional procedures.[5]

However, the place of MIDCAB in the array of cardiac procedures has yet to be determined. Concerns remain whether such a technically demanding operation may provide a real benefit when compared with conventional revascularization techniques such as coronary artery bypass grafting (CABG) [6] or percutaneous transluminal coronary angioplasty (PTCA).[7]

New information on the long-term results of MIDCAB, as well as the knowledge of major determinants of outcome, may be helpful to establish the real efficacy of this operation and its place as a stand-alone

TABLE I.—*Preoperative data.*

Variable	Value
Mean age (yrs)	60.2±10.1
Sex (male)	85 (78%)
Previous MI	59 (54.1%)
LVEF<50%	9 (8.3%)
Insulin-dependent diabetes mellitus	7 (6.4%)
Renal insufficiency	13 (11.9%)
COPD	19 (17.4%)
Cerebrovascular disease	11 (10.1%)
Malignancies	12 (11.0%)
Coronary lesions	
1-vessel disease	75 (68.8%)
2-vessel disease	26 (23.8%)
3-vessel disease	8 (7.3%)

MI: myocardial infarction; LVEF: left ventricular ejection fraction; COPD: chronic obstructive pulmonary disease.

therapy or as an adjunct to hybrid procedures in LAD revascularization. With this study, we retrospectively investigated variables related to long-term outcome in a series of consecutive patients operated between 1997 and 2005.

Material and methods

Patients

From March 1997 to October 2005, 109 patients (mean age 60.2±10.1 years, range 25-82) underwent myocardial revascularization on a beating heart through a left anterior small thoracotomy. Preoperative data are shown in Table I. Previous myocardial infarction was noted in 59 patients (54.1%) and moderate left ventricular dysfunction (left ventricular ejection fraction [LVEF] <50%) in 9 (8.2%). All operations were elective; the procedure was a redo operation in 2 (1.8%).

Inclusion criteria

MIDCAB was performed chiefly for isolated LAD disease (75/109; 68.8%) in which PTCA was unadvisable, unsuccessful or impossible. In those patients (34/109; 31.2%) with multivessel coronary artery disease, MIDCAB on LAD was performed for: severe contraindication to sternotomy (2/109; 1.8%); hybrid revascularization (6/109; 5.5%); not graftable poor peripheral bed (11/109; 10.1%), coronary artery into a previous infarcted area (17/109; 15.6%).

Special attention was paid to the anatomic features of the LAD at angiography. Intramyocardial, calcified or small-sized (<1.5 mm) LAD were considered anatomic contraindications to MIDCAB.

Operative technique

Surgical techniques significantly changed over the 8 years of the study period. A conventional single lumen endotracheal tube was used in all patients. The chest was opened *via* a small (8-10 cm) left anterior thoracotomy in the fourth or fifth intercostal space. The pleural cavity was opened routinely and a moist sponge was used to partially collapse the left lung. Left internal mammary artery (LIMA) to LAD anastomoses were performed with a 7/0 or 8/0 running polypropylene suture.

In the first 47 cases (February 1997 to December 1998), the LIMA was directly harvested through the thoracotomy for the distal segment or indirectly through a thoracoscope (Olympus, Hamburg, Germany) for the proximal portion, as previously described.[4] Local immobilization of the anastomotic site was achieved using epicardial 5/0 polypropylene sutures placed twice to surround the LAD proximally and distally to the target site.

Since 1999 (starting with case 48), when use of a special spreader and a myocardial wall stabilizer (Autosuture International Inc., Norwalk, CT, USA) was instituted, complete LIMA harvesting was done under direct vision and a motionless anostomosis.

Since June 1999 (starting with case 63), we have routinely used intracoronary shunts (Medtronic Inc., Minneapolis, MN, USA) that make LAD occlusion unnecessary.

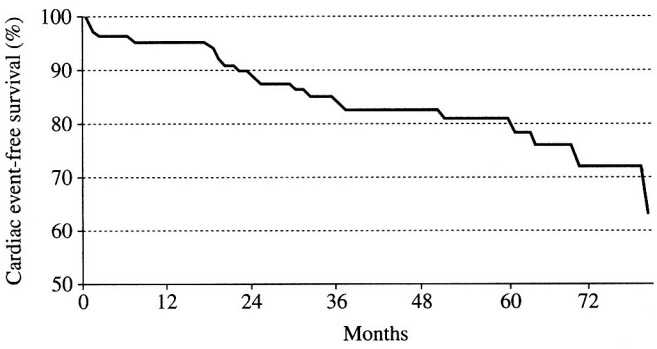
Angiographic reinvestigation and follow-up

The first 57 patients (53.2%) underwent early postoperative angiographic reinvestigation of LIMA to LAD grafts within 1 month after surgery. All 109 patients were subsequently followed up at our outpatient clinic. The follow-up was completed in 100% of patients (mean 50.7 months, range 3-93). During the follow-up period, a prospective evaluation of repeated LAD revascularization and new cardiac events (recurrence of angina, acute myocardial infarction, new revascularization procedures, whether percutaneous or surgical) was conducted. All events were source-documented and adjudicated by consensus of

TABLE II.—*Early results.*

Variable	Value
Death	0
Stroke	0
Perioperative MI	2 (1.8%)
Redo for bleeding	3 (2.7%)
Patients transfused	8 (7.3%)
Atrial fibrillation	10 (9.1%)
Hospital stay (days)	5.8±1.3
LIMA-LAD patency rate	56/57 (98.2%)
LIMA-LAD perfect patency rate	54/57 (94.7%)
Early LAD revascularization	3 (2.7%)
Redo CABG	2 (1.8%)
PTCA	1 (0.9%)

MI: myocardial infarction; LIMA: left internal mammary artery; LAD: left anterior descending coronary artery; CABG: coronary artery bypass graft; PTCA: percutaneous transluminal coronary angioplasty.



Months follow-up	0	12	24	36	48	60	72
Patients at risk	109	87	78	69	48	38	29

Figure 1.—Cardiac event-free survival.

two reviewers (PT and GP). Late coronary angiography was performed selectively on patients presenting signs of recurrent myocardial ischemia.

Statistical analysis

Plus-minus values are the mean ±SD or median and range when appropriate.

Event-free survival was calculated using Kaplan-Meier analysis. Determinants of long-term outcome (LAD revascularization and new cardiac events) were identified using a Cox proportional hazards regression model. Predictors in this analysis were: sex, age, LVEF <50%, insulin-dependent diabetes mellitus, multivessel coronary artery disease, operation performed before 1999. Probability values below 0.05 were considered as significant. All analyses were performed using the SAS statistical package v8 (SAS Institute, Cary NC, USA).

Results

In-hospital outcome

Early clinical results are shown in Table II. The procedure was converted into sternotomy in 1 case (0.9%). No deaths occurred. Two patients (1.8%) experienced a perioperative myocardial infarction; 3 (2.7%) were reoperated for bleeding; 8 were transfused (7.3%); 10 (9.1%) experienced transient postoperative atrial fibrillation. No patients had renal or respiratory acute insufficiency. The mean postoperative length of stay was 5.8±1.3 days.

Early postoperative angiographic reinvestigation was conducted in patients operated on without the use of myocardial wall stabilization devices. We found 1 (0.9%) LIMA-LAD anastomotic occlusion and 2 (1.8%) LIMA-LAD anastomotic significant stenoses (>50%). The anastomotic perfect patency rate was 54/57 (94.7%). All 3 patients had undergone early LAD repeated revascularization: 2 were reoperated with recycling of the LIMA graft, a percutaneous coronary angioplasty was successfully performed in the third.

Follow-up

During the follow-up period, 4 patients died at 24, 32, 41 and 63 months, respectively, because of extracardiac causes. Survival was 100% and 95.8% at 1 and 5 years, respectively. Recurrent myocardial ischemia occurred in 16 patients (14.7%) at a mean of 38.7±16 months (range 1-80) after surgery; acute myocardial infarction occurred in 1 (0.9%) at 42 months after surgery. Freedom from acute myocardial infarction and recurrent angina were 98.4±1.6% and 98.4±1.6% at 1 year, 98.4±1.6% and 91.8±4.8% at 3 years and 96.6±2.2% and 91.8±4.8% at 5 years, respectively.

Cardiac event-free survival was 95.3% and 80.8% at 1 and 5 years, respectively (Figure 1, Table III). At multivariable analysis, moderate left ventricular dysfunction and female sex were the only predictors affecting long-term cardiac outcome (hazard ratio

TABLE IV.—*Determinants of late cardiac-related events (Cox proportional-hazards regression model).*

Variable	Hazard ratio	95% CI	P value
Operation before 1999	0.35	0.09-1.32	0.121
Moderate LV dysfunction	5.10	1.97-13.22	<0.001
Age	1.01	0.96-1.06	0.617
Female sex	29.35	7.68-112.23	<0.001
Multivessel disease	0.66	0.22-1.96	0.460

LV: left ventricular.

[HR] 5.1; P<0.001, and HR 29.35; P<0.001), respectively (Table IV, Appendix I).

During the follow-up period, at a mean of 39.7±18 months, 17 patients underwent angiographic reinvestigation, 14 for recurrent myocardial ischemia and 3 before valve replacement. New coronary lesions developed in 12, in 5 of which LAD and/or LIMA were involved: 1 had a significant lesion at the LIMA-LAD anastomotic site, 1 a LIMA string sign, and 3 had new lesions proximally or distally to the anastomotic site. The remaining 7 had new coronary lesions in coronary vessels other than LAD. Globally, 9 patients (8.3%) underwent revascularization during the follow-up period: 4 coronary artery bypass grafts (CABG) and 5 PTCA. When 3 early procedures were included, 12 patients (11%) needed further revascularization after MIDCAB at 5 years after the operation (Table V). Cumulative freedom from repeated revascularization was 95.3% and 88.3% at 1 and 5 years, respectively (Figure 2, Table VI). Five patients (4.6%) underwent late repeated LAD revascularization: 4 redo-CABG and 1 PTCA. When included in the early in-hospital postoperative period, 8 patients (7.3%) required repeated revascularization on LAD at 5 years after MIDCAB. Freedom from LAD repeated revascularization, including the early postoperative period, was 95.3% and 91.6% at 1 and 5 years, respectively (Figure 2). At multivariable analysis (Cox regression), women were found to have a higher risk of repeated LAD revascularization (HR 30.24; P<0.001) (Table VII, Appendix II).

Discussion

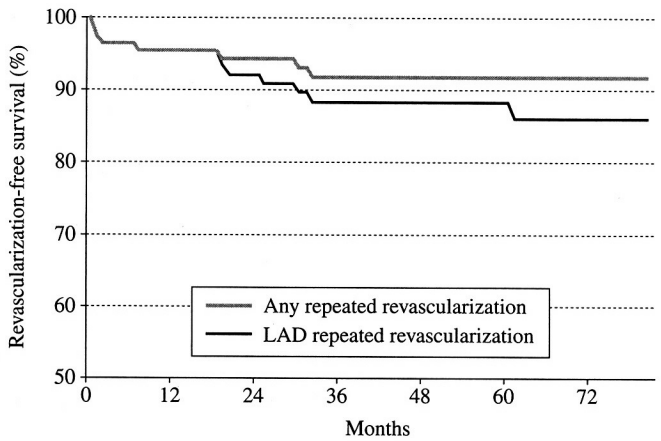
Although satisfactory early-mid-term clinical and angiographic results have been variously reported,[1-4] initial enthusiasm about the effectiveness of MIDCAB to revascularize the left anterior coronary artery has given way to caution.[7,8] A variety of reasons explain this change in views. First, there was some ambiguity surrounding the role of MIDCAB as a competitor to conventional surgery *versus* percutaneous revascularization.[9] Second, a broad disparity in patient selection—one-vessel *vs.* multivessel disease, elective *vs.* necessity criteria, low *vs.* high-risk patients—clouded the real efficacy of this operation and its place as a stand-alone therapy or as an adjunct to hybrid procedures in LAD revascularization.

In our 8-year series, all patients referred for MIDCAB were carefully selected. Great attention was paid to LAD anatomic features and to patient characteristics. A favourable LAD and chest anatomy were considered

TABLE V.—*Early and late repeated revascularizations.*

Patient	Months	Angiographic lesions	Treatment	Target vessels
B. C.	1	LIMA-LAD (stenosis)	PTCA	LAD
L. L.	1	LIMA-LAD (stenosis)	CABG	LAD
M. E.	1	LIMA-LAD (occlusion)	CABG	LAD
P. T.	2	LIMA-LAD (occlusion)	CABG	LAD
M. M.	7	LIMA-LAD (stenosis)	CABG	LAD
B. C.	19	LAD (new lesion)	PTCA	LAD
P. F.	19	Cx, RCA (new lesions)	PTCA	Cx, RCA
G. B.	20	Cx (progression of subcritical lesions)	PTCA	Cx
P. C.	25	RCA (progression of subcritical lesion)	PTCA	RCA
E. W.	30	LIMA (string sign), Cx, RCA (new lesions)	CABG	LAD, Cx, RCA
C. S.	32	LIMA-LAD (stenosis), RCA (new lesion)	CABG	LAD, RCA
G. A.	61	Cx (new lesion)	PTCA	Cx

LIMA: left internal mammary artery; LAD: left anterior descending coronary artery; Cx: circumflex coronary artery; RCA: right coronary artery; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft.



Months follow-up	0	12	24	36	48	60	72
Patients at risk for any and LAD revasculization	109	87	78	68	51	39	27

Figure 2.—Revascularization-free survival.

mandatory. An isolated non-PTCA treatable LAD lesion was the main indication for surgery. Admittedly, incomplete revascularization is one of the main variables affecting long-term outcome after CAB surgery.[10] According to this view, patients with a multivessel disease were considered eligible for MIDCAB if not amenable to complete revascularization or, in selected cases, in case of a hybrid procedure.

Generally speaking, our data confirm the known good early outcome of MIDCAB.[1-3] No in-hospital deaths and very low morbidity were observed. The conversion rate to sternotomy was negligible. Early angiographic reinvestigation also showed satisfactory results (98.2% and 94.3% LIMA to LAD patency and perfect patency, respectively). This is in line with published data[2, 8, 11-13] and compares favourably with early patency rates reported for conventional CABG [11, 14] and off-pump coronary artery bypass (OPCAB).[8, 15] It is noteworthy that these results were obtained in the first half of our series, in which graft patency may have been affected by both the learning curve and the absence of dedicated devices (wall stabilizers, intracoronary shunts).[13]

Our data confirm the feasibility, safety and reliability of MIDCAB. However, in the words of one operator, "just because something can be done does not automatically means that it should be done."[6] MIDCAB

TABLE VII.—*Determinants of late repeated revascularization on LAD (Cox proportional-hazards regression model).*

Variable	Hazard ratio	95% CI	P value
Operation before 1999	1.24	0.19-7.94	0.824
Moderate LV dysfunction	4.62	0.82-25.95	0.082
Age	0.97	0.89-1.05	0.426
Female sex	30.24	5.31-172.22	<0.001
Multivessel disease	0.85	0.18-4.07	0.835

remains a technically demanding operation, requiring an experienced surgeon and dedicated programs.[6, 8] Moreover, long-term results are not yet well established.[6]

Therefore, in order to ascertain the real value of MIDCAB, its feasibility needs to be followed by established long-term effectiveness. In the future, MIDCAB will be chiefly employed as a platform for multiple revascularizations in selected patients or as an adjunct to PTCA in hybrid procedures.[16, 17] In this way, a better understanding of variables related to general and cardiac survival and to freedom from LAD and cumulative revascularization may be helpful for patient selection.

Our cumulative 5-year survival was excellent and compares well with other series with shorter follow-up periods,[1, 18] suggesting that in selected patients MIDCAB offers a satisfactory mid-term clinical outcome. No cardiac-related deaths were observed in our study; accordingly, the determinants of cumulative survival could not be identified. The incidence of subsequent LAD revascularization was also satisfactory (freedom rates of 95.3% and 91.6% at 1 and 5years, respectively). Previous studies have shown similar results at 1 year after operation,[3] whereas longer-scale data are currently missing. Our 5-year LAD patency rate also compares favourably with conventional CAB.[19, 20] Interestingly, 4/8 repeated procedures on LAD occurred within 3 months of MIDCAB and fell within the first part of our study period, in which the learning curve could have played a negative role. This may imply that, as previously suggested,[3, 13] MIDCAB in the era of dedicated devices may further improve early and late graft patency.

Multivariate analysis supported evidence for female sex as an independent risk factor for repeated revascularization on LAD. Again, it is likely that vessel size may have affected the quality of anastomosis, particularly in the absence of proper wall stabilization. Female sex is thought to affect anastomotic patency

also in conventional CAB, although no conclusive evidence has been reported.[21, 22] In the attempt to improve graft patency, beating-heart minimally invasive procedures could benefit from new distal automatic anastomotic devices.[23]

One- and 5-year cumulative freedom from cardiac events was 95.3% and 80.8%, respectively. Other MIDCAB series found similar results.[12, 18, 24] Occurrence of acute myocardial infarction and recurrent angina during the follow-up period was satisfactory, perhaps partially reflecting the relatively low percentage of patients with multivessel disease. New cumulative cardiac-related events were found to be influenced by two variables: female sex and moderate left ventricular dysfunction. Similar observations have been reported by studies on long-term outcome after conventional CABG. In our series, the presence of multivessel disease did not directly affect cardiac outcome; nonetheless, reduced long-term event-free survival has recently been linked with the extent of coronary artery disease.[24] Of our 34 patients with multivessel disease, only 1/3 effectively received an incomplete revascularization. Our data are therefore inadequate to ascertain the effectiveness of functional revascularization in patients with multivessel coronary disease and may underestimate the prognostic value of complete revascularization in these patients.

Limitations of the study

We recognize limitations in the design and the interpretation of this study—it is a retrospective single center observational analysis. Moreover, the small study population may not have allowed the detection of additional factors related to survival, cardiac morbidity or graft patency.

Conclusions

Our study shows that MIDCAB is a safe strategy to revascularize the left anterior coronary artery and has a 5-year outcome comparable to that of conventional CABG. According to our and others' results,[8, 25] careful and appropriate patient selection and the use of dedicated devices are important. Special attention should be reserved for female patients who appear to have a worse cardiac outcome and a higher probability of repeated revascularization on LAD. In multivessel coronary artery disease, MIDCAB may offer a viable option when a complete revascularization is not feasible or a hybrid procedure is envisaged.

Larger studies with longer follow-up periods are needed to better assess the advantages and limitations of MIDCAB in the array of surgical revascularization strategies.

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APPENDIX I

The SAS System - The PHREG Procedure

Model Information of Cox regression analysis of cardiac event-free survival

Data Set TAR.MID165
Dependent Variable MESIEVEN
Censoring Variable EVENTFREE
Censoring Value(s)' O

Ties Handling BRESLOW

Summary of the number of events and censored values

Total	Event	Censored	Percent censored
109	22	87	79.821

Convergence status

Convergence criterion (GCONV=1 E-8) satisfied.

Model Fit Statistics

	Without covariates	With covariates
-2 LOG L	177.193	148.998
AIC	177.193	158.998
SBC	177.193	164.453

Testing Global Null Hypothesis: BETA=O

	Test	χ^2DF	Pr > χ^2
Likelihood Ratio	28.1951	5	<0.0001
Score	50.1207	5	<0.0001
Wald	29.7568	5	<0.0001

APPENDIX II

The SAS System - The PHREG Procedure

Model Information of Cox regression analysis for LAD repeated revascularization

Data Set TAR.MID165
Dependent Variable MESIEVEN
Censoring Variable RIVAFREE
Censoring Value(s)' O

Ties Handling BRESLOW

Summary of the number of events and censored values

Total	Event	Censored	Percent censored
109	08	101	92.66

Convergence status

Convergence criterion (GCONV=1 E-8) satisfied.

Model Fit Statistics

	Without covariates	With covariates
-2 LOG L	72.579	52.914
AIC	72.579	62.914
SBC	72.579	63.311

Testing Global Null Hypothesis: BETA=O

	Test	χ^2DF	Pr > χ^2
Likelihood ratio	19.6651	5	<0.0014
Score	42.5932	5	<0.0001
Wald	21.0065	5	<0.00008