Myocardial revascularization with and without cardiopulmonary bypass in multivessel disease patients

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Key words:
Cardiopulmonary bypass; Coronary artery surgery; Myocardial revascularization.

Background. **Off-pump coronary artery bypass surgery is widely performed because of its proved safety, but its effectiveness remains controversial. The aim of this retrospective study was to compare early and late results in patients with multivessel disease, operated on off-pump and on-pump.**

Methods. **From November 1994 to December 2001, 2957 patients with multivessel disease underwent isolated coronary revascularization, on-pump (n = 1924) and off-pump (n = 1033). Sixty-five patients (2.2%) who were converted from off-pump to on-pump were considered as part of the off-pump group.**

Results. **Stepwise logistic regression analysis showed that the use of cardiopulmonary bypass was an independent predictor for early death, early negative primary endpoints, and early major events. Conversion to on-pump was an independent risk factor for a higher incidence of death due to any cause and cardiac death, early negative primary endpoints, and early major events. Conversion, however, did not affect late clinical outcome. The 6-year freedom from death (any cause, cardiac cause), myocardial infarction, redo/coronary angioplasty and any events was similar in the two groups.**

Conclusions. **These results suggest that off-pump surgery reduces early mortality and morbidity. These benefits are not at the expense of the long-term clinical outcome which seems to be similar in the two groups. Patients who require conversion from off-pump to on-pump have a much higher mortality and morbidity although this does not seem to influence their long-term clinical outcome.**

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Introduction

Many authors showed that off-pump surgery reduces the systemic inflammatory response[1-3], myocardial injury due to ischemia during cardioplegic arrest[3,4], and early mortality[5] and morbidity[5-7]. However, the long-term results of off-pump surgery have not been clearly investigated[6-8]. The aim of this retrospective study was to compare off-pump and on-pump coronary surgery in patients with multivessel disease, analyzing both the early and late clinical results.

Methods

From November 1994 to December 2001, 2957 patients with multivessel disease underwent isolated coronary revascularization, with cardiopulmonary bypass (CPB) in 1924 cases (on-pump group) and without CPB in 1033 (off-pump group). Sixty-five patients (2.2%) who were converted from off-pump to on-pump were considered as part of the off-pump group (intention to treat).

Patient selection. The main contraindications to off-pump coronary surgery were the vessel size (> 1.2 mm) and the absence of widespread coronary calcifications. In the presence of mechanical and/or electrical instability the patient was selected preferably for on-pump surgery. The final decision was made on the basis of the expertise of the surgeon responsible for the operation.

Surgical technique. *On-pump.* CPB was instituted by cannulation of the ascending aorta and right atrium. A standard circuit with a hollow five-membrane oxygenator and a roller pump was used. The body temperature was kept at 37°C. Myocardial protection was achieved by means of intermittent antegrade warm blood cardioplegia[9].

Off-pump. The method of exposure of the target coronary vessel and of stabilization has been reported previously[10]. In the most

recent years, apical suction was used for better exposure, in particular of the lateral and the inferior walls (Xpose™, Guidant Corporation, Cupertino, CA, USA). When the coronary artery was exposed, stabilization was achieved using a pressure (Acces Ultima™ System, Guidant Corporation) or suction (Axius Vacuum 2™ System, Guidant Corporation) stabilizer. The target vessel was occluded using a 4/0 prolene suture, passed on a small piece of silicone tubing and then gently snared.

Clinical data collection, monitoring and definition. A set of perioperative data are collected prospectively for all patients undergoing coronary artery bypass grafting at our institution. The following were recorded and defined:
- mortality including death due to any cause;
- cardiac mortality including any death due to cardiac causes and sudden deaths;
- a cerebrovascular accident was defined as a global or focal neurological deficit, diagnosed by a neurologist and confirmed by a brain computed tomography scan;
- acute myocardial infarction (AMI) was defined as enzymatic elevation, ECG signs of necrosis, new akinetic segment(s) at echocardiography and ventricular, non-K^+-related arrhythmias;
- early major events were defined as the sum of death due to any cause, cerebrovascular accidents, AMI, low output syndrome (need of intra-aortic balloon pump and/or inotropic drugs for more than 12 hours), need of mechanical ventilation for more than 24 hours, acute renal failure (postoperative blood creatinine ≥ 2.0 mg%, if the preoperative value was normal [≤ 1.4] or 1 mg higher if pathologic) and gastrointestinal complications;
- early negative primary endpoints were defined as death due to any cause, AMI and cerebrovascular accidents;
- any event was defined as death due to any cause, AMI in any territory and redo/coronary angioplasty in any territory.

Follow-up. All the patients were followed up in our outpatient clinic 3, 6 and 12 months after surgery and thereafter at yearly intervals. The most recent information was obtained by phone interview with the patient or referring cardiologist. Follow-up data up to December 31, 2002 were 100% complete.

Statistical analysis. Results are expressed as mean value ± SD. Statistical analysis comparing the two groups was performed with unpaired two-tailed Student's t-testing for the means or using the χ^2 test for categorical variables. Patients converted to on-pump were compared with patients who underwent the procedure as scheduled. Stepwise logistic regression was used to select the independent variables (from a set of already reported preoperative variables[5]) that could predict the endpoints of this study and included all the univariate variables with a p value ≤ 0.2. In the final regression model, independent variables were expressed as odds ratio (OR) with the respective 95% confidence limits (CL); the related p value was also reported. Actuarial curves were obtained with the Kaplan-Meier method. Statistical significance was calculated using the log-rank test. Cox analysis was used to evaluate the independent risk factors for reduced late events. In the Cox analysis model, independent variables were expressed as hazard ratios with the respective 95% CL; the related p value was also reported. The SPSS software (Chicago, IL, USA) was used. A p value ≤ 0.05 was considered as statistically significant.

Results

Preoperative and operative data. The two groups were similar for most of the preoperative characteristics. Patients scheduled for off-pump coronary surgery were older. The incidence of chronic obstructive pulmonary disease and that of extracardiac vasculopathy were higher in the off-pump group. The extent of surgical coronary disease and the number of urgent procedures and reoperations were higher among patients who underwent myocardial revascularization with CPB (Table I). The technical aspects are shown in table II.

Early results. The 30-day mortality was 2.5%, 1.5% in the off-pump and 3.0% in the on-pump group (p = 0.018). There were no differences between the two groups with regard to cardiac deaths, cerebrovascular accidents and AMI. Both the early negative primary endpoints and early major events were lower in the off-pump group. The transfusion rate, postoperative atrial fibrillation incidence and creatine kinase-MB mean peak values were higher in the on-pump group (Table III).

Patients who underwent myocardial revascularization without CPB had a significantly shorter postoperative stay, both in the intensive care unit (14.2 ± 16.6 vs 19.5 ± 23.3 hours, p < 0.001) and in the ward (4.4 ± 2.7 vs 5.3 ± 3.9 days, p < 0.001).

Table IV shows the independent predictors of higher incidence of 30-day events. On-pump surgery was found to be an independent risk factor for death, early negative primary endpoints and early major events.

Sixty-five patients were converted to on-pump; the causes of conversion were technical in 9 and related to hemodynamic instability in 56. Converted patients were compared with those who underwent the procedure as scheduled. The preoperative characteristics were similar except for the mean age (68.2 ± 9.1 years in converted patients vs 63.6 ± 9.4 years in the remaining group, p < 0.001).

Stepwise logistic regression showed that age (continuous, OR 1.05, CL 1.02-1.09, p = 0.0001) and ejection fraction ≤ 35% (OR 2.2, CL 1.1-4.7, p = 0.0422) were independent predictors of conversion.

Table I. Preoperative data.

	Off-pump (n=1033)	On-pump (n=1924)	p
Age (years)	64.5 ± 9.4	63.4 ± 9.4	0.001
Female gender	168 (16.3%)	335 (17.4%)	NS
Diabetes	233 (22.6%)	474 (24.6%)	NS
Chronic obstructive pulmonary disease	72 (7.0%)	85 (4.4%)	0.003
Chronic heart failure	19 (1.8%)	43 (2.2%)	NS
Chronic renal failure	34 (3.3%)	45 (2.3%)	NS
Extracardiac vasculopathy	265 (25.7%)	413 (21.5%)	0.010
Redo	14 (1.4%)	143 (7.4%)	< 0.001
Unstable angina	334 (32.3%)	658 (34.2%)	NS
Urgency	217 (21.0%)	502 (26.1%)	0.002
Left main disease	172 (16.7%)	310 (16.1%)	NS
Two-vessel disease	716 (69.5%)	1014 (52.7%)	< 0.001
Three-vessel disease	316 (30.9%)	910 (47.3%)	< 0.001
Ejection fraction (%)	58.3 ± 13.0	57.0 ± 13.4	NS
EuroSCORE	4.1	4.1	NS

Table II. Technical details.

	Off-pump (n=1033)	On-pump (n=1924)	p
Carotid endarterectomy	20 (1.9%)	38 (2.0%)	NS
Anastomoses/patient	2.6 ± 0.7	3.0 ± 0.9	< 0.001
Left internal mammary artery	1005 (97.3%)	1813 (94.2%)	< 0.001
Right internal mammary artery	605 (58.6%)	1214 (63.1%)	0.016
Right gastroepiploic artery	57 (5.5%)	314 (16.3%)	< 0.001
Radial artery	67 (6.5%)	154 (8.0%)	NS
Inferior epigastric artery	5 (0.5%)	13 (0.7%)	NS
Saphenous vein graft	585 (56.6%)	957 (49.7%)	< 0.001
Sequential graft	225 (21.8%)	868 (45.1%)	< 0.001

Table III. Early clinical outcome.

	Off-pump (n=1033)	On-pump (n=1924)	p
Deaths	16 (1.5%)	57 (3.0%)	0.018
Cardiac deaths	12 (1.2%)	34 (1.8%)	NS
Cerebrovascular accident	9 (0.9%)	24 (1.2%)	NS
Acute myocardial infarction	10 (1.0%)	31 (1.6%)	NS
Early negative primary endpoints	28 (2.7%)	82 (4.3%)	0.033
Low output syndrome	13 (1.3%)	69 (3.6%)	< 0.001
Acute renal failure	9 (0.9%)	17 (0.9%)	NS
Acute respiratory failure	3 (0.3%)	16 (0.8%)	NS
Abdominal complications	2 (0.2%)	8 (0.4%)	NS
Early major events	65 (6.3%)	159 (8.3%)	0.043
Bleeding (ml/12 hours)	446 ± 457	495 ± 373	0.003
Transfused patients	261 (25.3%)	580 (30.1%)	0.005
Creatine kinase-MB peak* (IU/l)	28.6 ± 49.1	44.4 ± 54.1	< 0.001
Postoperative atrial fibrillation	116 (11.2%)	274 (14.2%)	0.021
Intensive care unit stay (hours)	14.2 ± 16.6	19.5 ± 23.3	< 0.001
In-hospital stay (days)	4.4 ± 2.7	5.3 ± 3.9	< 0.001

* in patients without acute myocardial infarction.

The rate of all the events investigated in table V, but postoperative atrial fibrillation, was higher among converted than among the remaining patients. Conversion to on-pump was an independent risk factor for a higher incidence of death (due to any cause and cardiac-related), early negative primary endpoints and early major events (Table IV).

Table IV. Independent predictors of 30-day events.

Variable	Death		Cardiac death		Cerebrovascular accident	
	OR (95% CL)	p	OR (95% CL)	p	OR (95% CL)	p
Age	1.03 (1.01-5.9)	0.282	–	–	–	–
CHF	3.2 (1.4-7.4)	0.0072	–	–	4.2 (1.3-13.2)	0.0157
Conversion to on-pump	3.6 (1.1-12.1)	0.0354	4.4 (1.5-12.8)	0.0056	–	–
Diabetes	1.7 (1.1-2.8)	0.0391	–	–	–	–
ECV	–	–	–	–	2.9 (1.5-5.9)	0.0024
EF ≤ 35%	3.1 (1.7-5.9)	0.0004	5.5 (2.8-10.9)	< 0.0001	3.6 (1.6-8.7)	0.0030
Female	1.8 (1.1-3.1)	0.0295	2.2 (1.2-4.3)	0.0110	–	–
On-pump	2.5 (1.1-3.9)	0.0356	–	–	–	–
Urgency	2.1 (1.3-5.9)	0.0023	2.5 (1.4-4.6)	0.0023	–	–
	AMI		ENPEP		EME	
	OR (95% CL)	p	OR (95% CL)	p	OR (95% CL)	p
Age	–	–	1.02 (1.01-1.05)	0.0208	1.03.1 (1.02-1.06)	< 0.0001
CHF	–	–	4.6 (2.3-9.3)	< 0.0001	3.9 (2.2-7.1)	< 0.0001
Conversion to on-pump	–	–	3.2 (1.4-7.2)	0.0048	6.1 (3.5-10.9)	< 0.0001
Diabetes	–	–	–	–	–	–
ECV	–	–	1.7 (1.1-2.5)	0.0157	1.4 (1.1-1.9)	0.0382
EF ≤ 35%	4.7 (2.2-9.8)	< 0.0001	3.3 (1.9-5.5)	< 0.0001	3.8 (2.6-5.7)	< 0.0001
Female	–	–	–	–	1.5 (1.1-2.1)	0.0153
On-pump	–	–	1.5 (1.1-2.8)	0.0333	1.3 (1.1-1.8)	0.0458
Urgency	2.8 (1.5-5.2)	0.0010	2.1 (1.4-3.1)	0.0003	1.9 (1.4-2.5)	< 0.0001

AMI = acute myocardial infarction; CHF = chronic heart failure; CL = confidence limit; ECV = extracardiac vasculopathy; EF = ejection fraction; EME = early major events; ENPEP = early negative primary endpoint; OR = odds ratio.

Late results. The length of follow-up ranged from 1 to 8.1 years (mean 3.9 ± 2.0 years). One hundred and twenty-one more patients died (4.2%), 52 (43.0%) of cardiac causes; 28 (1.0%) had a new AMI, 53 (1.8%) had a redo operation or coronary angioplasty, and 174 (6.1%) any event. Table VI shows the 6-year actuarial results and table VII the independent risk factors identified at Cox analysis. On-pump and conversion to on-pump were no longer risk factors.

Discussion

In view of its proven safety, off-pump coronary surgery is nowadays routinely performed in most cardiac surgery centers. However, its effectiveness as compared to that of conventional on-pump coronary surgery is still subject of debate.

In a previous retrospective study of ours[5], we demonstrated that CPB was independently associated

Table V. Thirty-day results in patients converted to on-pump (C) vs those in whom the procedure was carried out as per schedule (NC).

	Group C (n=65)	Group NC (n=2892)	p
Deaths	6 (9.2%)	67 (2.3%)	0.005
Cardiac deaths	4 (6.2%)	42 (1.5%)	0.017
Cerebrovascular accident	3 (4.6%)	30 (1.0%)	0.035
Acute myocardial infarction	3 (4.6%)	38 (1.3%)	0.050
Early negative primary endpoints	8 (12.3%)	102 (3.5%)	0.002
Low output syndrome	5 (7.7%)	77 (2.7%)	0.033
Early major events	22 (33.8%)	202 (7.0%)	< 0.001
Bleeding (ml/12 hours)	600 ± 353	475 ± 406	0.025
Transfused patients	33 (50.8%)	808 (27.9%)	< 0.001
Creatine kinase-MB peak* (IU/l)	73.0 ± 91.6	38.4 ± 51.9	0.015
Postoperative atrial fibrillation	13 (13.0%)	377 (13.0%)	NS
Intensive care unit stay (days)	40.0 ± 50.0	17.3 ± 20.2	0.018
In-hospital stay (days)	5.2 ± 2.5	5.0 ± 3.6	NS

* in patients without acute myocardial infarction.

Table VI. Six-year actuarial results.

Freedom from	Off-pump (n=1033)	On-pump (n=1924)	p
Death due to any cause	93.7 ± 0.9	90.9 ± 0.8	NS
Cardiac death	97.1 ± 0.8	95.2 ± 0.6	NS
AMI	97.7 ± 0.7	96.1 ± 0.6	NS
Redo/PTCA	96.8 ± 1.2	96.9 ± 0.6	NS
Any event	90.5 ± 1.4	88.0 ± 0.9	NS

AMI = acute myocardial infarction; PTCA = coronary angioplasty.

with an increased early mortality, cerebrovascular accident incidence and early major events. Sabik et al.[10] did not find any mortality difference even though this was twice higher among patients operated on-pump compared to those operated off-pump.

Recently, a reduction in morbidity but not in mortality has been demonstrated in two randomized studies comparing patients operated on-pump and off-pump[6,7]. Given that the incidence of major morbidity after coronary revascularization (i.e. cerebrovascular accidents, AMI, etc.) is relatively small, studies with large numbers of patients would be necessary to determine the significance of any differences in these outcomes.

In this study a large cohort of patients has been analyzed, demonstrating that off-pump coronary surgery is associated with a decrease in the 30-day mortality, incidence of early negative primary endpoints and of major events (Table IV).

In the present study, we also evaluated secondary endpoints such as postoperative transfusion rate, atrial fibrillation and length of hospitalization (both in the intensive care unit and in the ward) which, as demonstrated by other reports[11-13], seem to be reduced when coronary surgery is performed off-pump.

A small percentage of patients who were operated off-pump had to be converted to on-pump, mostly because of hemodynamic instability. Conversion to on-pump seemed to carry a significantly higher early mortality and morbidity in this group of patients, probably a reflection of the learning curve. There is no evidence of its impact on late results.

There are not many reports in the literature which have studied mid- and long-term clinical results in patients who have undergone off-pump surgery. Gundry et al.[8] reported that the 7-year actual survival was the same in both groups (80% on-pump vs 79% off-pump), but the price to pay for off-pump revascularization was a 3-fold higher rate of reintervention (7% on-pump vs 20% off-pump). The main criticism of this paper is that most of the surgery was conducted in the early '90s when techniques, in particular with regard to exposure and stabilization, were rather crude and certainly not even remotely comparable to the ones which have been developed over the last few years.

Table VII. Cox analysis.

Variable	Freedom from									
	Death due to any cause		Cardiac death		AMI		Redo/PTCA		Any event	
	OR (95% CL)	p	OR (95% CL)	p	OR (95% CL)	p			OR (95% CL)	p
Age	1.04 (1.01-1.05)	< 0.0001	1.04 (1.01-1.07)	0.0006	1.03 (1.01-1.06)	0.0283	–		1.02 (1.01-1.04)	0.0031
CHF	2.1 (1.1-3.8)	0.0108	2.6 (1.3-5.4)	0.0078	–	–	–		1.9 (1.1-3.4)	0.0287
CRF	–	–	–	–	–	–	–		1.8 (1.1-3.2)	0.0330
Diabetes	1.7 (1.2-2.3)	0.0005	1.8 (1.2-2.8)	0.0038	–	–	–		1.4 (1.1-1.9)	0.0120
ECV	–	–	–	–	–	–	–		1.5 (1.1-1.9)	0.0041
EF ≤ 35%	3.2 (2.2-4.7)	< 0.0001	3.6 (2.2-5.9)	< 0.0001	3.8 (2.1-6.9)	< 0.0001	–		2.4 (1.7-3.5)	< 0.0001
Redo	2.2 (1.4-3.5)	0.0004	2.4 (1.3-4.4)	0.0044	2.2 (1.1-4.6)	0.0391	–		1.8 (1.2-2.8)	0.0040
Urgency	2.1 (1.2-3.8)	0.0015	2.0 (1.3-3.0)	0.0009	1.7 (1.1-2.8)	0.0290	–		1.6 (1.2-2.0)	0.0008

AMI = acute myocardial infarction; CHF = chronic heart failure; CL = confidence limit; CRF = chronic renal failure; ECV = extracardiac vasculopathy; EF = ejection fraction; OR = odds ratio; PTCA = coronary angioplasty.

More recently Angelini et al.[6] have analyzed the mid-term results in a randomized study. They suggested that the early benefits obtained with off-pump in terms of morbidity are not at the expense of a reduced long-term patency rate. Similar results at 1 year of follow-up were presented by Nathoe et al.[7]. In accordance with these authors, in our analysis we found that the 5-year actual outcome was identical regardless of whether patients had undergone on-pump or off-pump revascularization.

In conclusion, this retrospective study conducted on a large cohort of patients shows that off-pump surgery, in patients selected in accordance with our inclusion criteria, reduces early mortality and morbidity. These benefits are not at the expense of the long-term clinical outcome which is similar in both groups. Patients who require conversion from off-pump to on-pump have a much higher mortality and morbidity although this does not seem to modify the long-term clinical outcome. The number of patients who require conversion may be reduced by adhering more strictly to the indications.

Limitations of the study. The main limitation of this study could be the difference in some of the preoperative and operative data. Regarding age, extracardiac vasculopathy and urgency, their confusing power has been limited by the utilization of multivariate analysis. In case of chronic obstructive pulmonary disease and redo, they are not risk factors for any of the analyzed events. The difference of anastomoses per patient has no impact on early and late results, especially on revascularization failure. However, further retrospective studies, applying a propensity score to achieve two groups of patients with similar preoperative and operative characteristics, or randomized studies analyzing large populations, could provide more strong evidence on the effectiveness of off-pump surgery.

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