



On- and off-pump coronary surgery and perioperative myocardial infarction: an issue between incomplete and extensive revascularization

Francesco Alamanni^{a,1}, Luca Dainese^{a,1}, Moreno Naliato^{a,1}, Sebastiana Gregu^{b,1},
 Marco Agrifoglio^{a,1}, Gian Luca Polvani^{a,1}, Paolo Biglioli^{a,1},
 Alessandro Parolari^{a,1,*}, for the Monzino OPCAB Investigators¹

^a Department of Cardiac Surgery, Unit for Clinical Research in Atherothrombosis, Centro Cardiologico Monzino I.R.C.C.S., University of Milan, Milan, Italy

^b Department of Anesthesia and Intensive Care, Centro Cardiologico Monzino I.R.C.C.S., University of Milan, Milan, Italy

Received 30 October 2007; received in revised form 18 March 2008; accepted 22 March 2008

Abstract

Objective: Complete myocardial revascularization is the standard for coronary artery bypass grafting. It has been shown, however, that off-pump coronary bypass surgery (OPCAB) may reduce completeness of revascularization without affecting perioperative myocardial infarction rates. We evaluated the influence of OPCAB on major postoperative events in a large consecutive cohort of patients, with special emphasis on risk factors for perioperative myocardial infarction. **Methods:** From 1995 to 2004, 5935 patients underwent isolated coronary bypass surgery; of these, 4623 (77.9%) and 1312 (22.1%) underwent on-pump coronary surgery (CABG) and OPCAB, respectively. Patients undergoing OPCAB were matched to patients undergoing CABG by propensity score; logistic regression analysis models were used to study predictors of perioperative myocardial infarction. **Results:** In matched pairs, postoperative mortality, myocardial infarction, stroke, and atrial fibrillation were similar between groups, while reoperation for bleeding, time on ventilator and red blood cell use were lower in patients undergoing OPCAB. The number of distal anastomoses was lower in patients undergoing OPCAB (2.2 ± 0.80 in OPCAB vs 2.9 ± 0.86 in CABG, $p < 0.001$), as well as complete revascularization rates (61.9% in OPCAB vs 90.0% in CABG, $p < 0.001$). Multivariate analyses, performed on preoperative and intraoperative variables, showed that both incomplete revascularization and increasing numbers of distal anastomoses (even when controlling for completeness of revascularization) were significant predictors of perioperative myocardial infarction, while CABG/OPCAB strategy did not influence it. **Conclusions:** The choice of surgical technique did not influence the occurrence of major perioperative complications and of myocardial infarction, which is negatively affected by incomplete or too extensive revascularization strategies.

© 2008 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Coronary artery bypass; Off-pump; Postoperative complications; Myocardial infarction; Factor analysis

1. Introduction

In the past 15 years there has been an increasing interest in off-pump coronary bypass surgery (OPCAB) that has become a well established alternative to the standard on-pump operation (CABG); nowadays, approximately 20–25% of coronary bypass procedures are performed off-pump in the United States [1].

Several studies comparing OPCAB with CABG are now available, although no clear-cut conclusion on the clinical benefit of off-pump surgery has been reached [2]. A number

of studies has shown that fewer grafts tend to be performed off-pump than on-pump, suggesting higher incomplete revascularization rates for patients undergoing OPCAB [3,4], although perioperative myocardial infarction rate seems to be similar with either technique [3,5].

In this study we have analyzed the impact of the choice of surgical strategy (CABG vs OPCAB) on major postoperative events in a large consecutive cohort of patients, with special emphasis on relations between cardiopulmonary bypass (CPB) use, completeness of revascularization, and perioperative myocardial infarction.

2. Patients and methods

2.1. Patients

From January 1995 to December 2004, 5935 patients underwent isolated coronary artery bypass surgery at Centro

* Corresponding author. Address: Department of Cardiac Surgery, University of Milan, Centro Cardiologico, Fondazione Monzino IRCCS, Via Parea, 4, 20138 Milan, Italy. Tel.: +39 02 580021; fax: +39 02 58011194.

E-mail address: alessandro.parolari@cardiologicomonzino.it (A. Parolari).

¹ See Appendix A for the list of members.

Cardiologico Monzino. According to surgeon choice, myocardial revascularization was performed off-pump in 1312 (22.1%) patients and on-pump in 4623 (77.9%) patients. On- and off-pump patients were contemporaneous and not sequential groups. All patients underwent revascularization through a median sternotomy. Patients undergoing coronary revascularization through a thoracotomy were excluded. However, patients who were converted from off-pump to on-pump bypass were retained ($n = 16$); thus, this represents an intent-to-treat study.

2.2. Surgical technique

All operations (CABG and OPCAB) were performed via a midline sternotomy, conduits were harvested, and all patients received a full heparin dose (3 mg/kg).

2.2.1. Surgical technique: off-pump

Coronary artery exposure was achieved with stay sutures applied on the left lateral side of pericardium or with deep pericardial stay sutures placed above the entry of the left lower pulmonary vein and laterally to the entry of the inferior vena cava. Distal anastomoses were constructed before proximal anastomoses. The left internal thoracic artery to left anterior descending coronary artery anastomosis was constructed first. Mechanical stability of the distal anastomosis area was achieved with a mechanical (earlier experience, up to 1998) or a suction (since 1999) stabilizer; target vessel hemostasis was obtained with proximal and distal vessel coronary occlusion with a single 4-0 polypropylene stitch (earlier experience, up to 1998) or with a soft plastic coronary flow-shunt (since 1999); no apical suction stabilizers were used during the time period of this study. Proximal anastomoses were constructed to the aorta with a tangential clamp. After completion of all anastomoses, heparin was reversed with protamine in a 1:1 ratio.

2.2.2. Surgical technique: on-pump

Standard cannulation for CPB was performed with ascending aortic cannulation and dual stage cannulation of the right atrium. A nonpulsatile roller or centrifugal pump, hollow-fiber oxygenator with integrated heat exchanger, arterial filter, open cardiectomy reservoir, and polyvinyl tubing system were used in all cases. Each operation was performed with moderate or tepid hypothermia and hemodilution. Blood flow during CPB was kept at >2.0 l/min/m², and hematocrit at 18–25%. Myocardial protection was achieved by the administration of cold, multidose crystalloid or blood cardioplegia infused either antegrade or retrograde or in combination on induction and every 20 min. Distal anastomoses were usually constructed first, and the proximal anastomoses were constructed to the ascending aorta with a tangential clamp. After the patient was weaned from CPB and decannulated, heparin was reversed with protamine in a 1:1 ratio.

2.3. Data collection

Patients were identified from the prospective computerized database and preoperative, operative, and postoperative variables (see Appendix B, Table B.1) were retrieved from this database whose use for research was approved by Centro

Cardiologico Monzino Institutional Review Board. Because this is a retrospective study with a large number of patients whose data had been collected over a long duration, the Institutional Review Board waived the requirement for informed consent on the condition that the subjects' identities were hidden before analytical procedures were performed.

2.4. Statistical analysis

Continuous variables are presented as means \pm 1 standard deviation, categorical variables as percentage.

2.4.1. Comparison of early outcomes between CABG and OPCAB by propensity-matched pairs

To minimize selection bias before comparing the on- and off-pump groups, we used propensity score matching [6]. A subject's propensity score is his or her probability of receiving the treatment (in this case, exposure to CPB) given his or her covariate profile. Our propensity scores were computed from a logistic regression model with forward stepwise selection of the 29 preoperative variables (see Appendix B, Table B.1) predicting exposure to CPB; the C-statistic of this model was 0.79. Using only the propensity score, CABG patients were matched to OPCAB patients by using a greedy matching strategy. For this, matching to five decimal points was initially performed, followed by 4-, 3-, 2-, and 1-decimal-point matching. Off-pump patients whose propensity scores deviated more than 0.10 from those of on-pump patients were considered unmatched. This yielded 1062 off-pump patients propensity matched to 1062 on-pump patients. Group differences in clinical variables between CABG and OPCAB were assessed by analysis of variance, Chi-square or Fisher's exact tests when indicated.

2.4.2. Predictors of perioperative myocardial infarction and of incomplete revascularization

Perioperative myocardial infarction was defined both in CABG and in OPCAB as positive results in at least two of the three different tests: the appearance of new (>0.03 s) or enlarging Q waves, elevation in the myocardial fraction of creatine kinase (CK-MB >70 IU/l), and newly developed regional wall motion abnormalities on echocardiography [7]. Incomplete revascularization was defined as failure to graft a coronary artery system with a 50% or greater stenosis or lack of grafts to both the left anterior descending and circumflex coronary artery systems with a 50% or greater left main coronary artery stenosis [3,8]. It was not considered necessary to bypass all obstructed marginal branches of the circumflex coronary artery or diagonal branches of the left anterior descending coronary artery for revascularization to be considered complete.

Logistic regression analysis was used to determine independent predictors of perioperative myocardial infarction, and 29 preoperative and six intraoperative variables (see Appendix B, Table B.1) were entered first into a univariate logistic regression analysis model. Variables with a p value less than 0.2 at univariate logistic regression analysis were further analyzed with multivariate logistic regression analysis with forward stepwise selection. Separate multivariate models were analyzed for all patients together, for patients undergoing surgery in more recent years (in order to

Table 1
Comparison of patient characteristics in the whole patient population

	On-pump (n = 4623)	Off-pump (n = 1312)	p-Value
Age (years)	64 ± 8.9	66 ± 9.5	<0.001
Male gender	3811 (82.4%)	1056 (80.5%)	0.105
Weight (kg)	75 ± 11.7	74 ± 12.0	0.006
Body surface area (m ²)	1.82 ± 0.17	1.81 ± 0.17	0.017
Urgent/emergent surgery	178 (3.9%)	36 (2.7%)	0.058
Hypertension	2804 (60.7%)	824 (62.8%)	0.158
Diabetes	1051 (22.7%)	265 (20.2%)	0.055
Redo-operation	123 (2.7%)	90 (6.9%)	<0.001
Previous stroke	77 (1.7%)	46 (3.5%)	<0.001
Carotid artery disease	349 (7.5%)	125 (9.5%)	0.020
Smoke	1870 (40.4%)	477 (36.4%)	0.007
COPD	425 (9.2%)	169 (12.9%)	<0.001
Previous MI	1876 (40.6%)	537 (40.9%)	0.820
Previous MI, less than 6 months	653 (14.1%)	171 (13.0%)	0.313
Atrial fibrillation	80 (1.7%)	22 (1.7%)	0.895
Dialysis	9 (0.2%)	10 (0.8%)	0.003
Preoperative IABP	16 (0.3%)	3 (0.2%)	0.781
NYHA functional class	2.0 ± 0.66	2.1 ± 0.66	0.158
Echocardiographic EF (%)	56 ± 11.2	57 ± 10.9	0.069
Serum creatinine (mg/dl)	1.1 ± 0.47	1.2 ± 0.65	0.037
Tuman score	1.9 ± 1.8	2.3 ± 1.9	<0.001
No. of diseased vessels	2.7 ± 0.49	2.4 ± 0.75	<0.001
Significant LMT stenosis	948 (20.5%)	235 (17.9%)	0.038
Significant LAD stenosis	4179 (90.4%)	1178 (89.8%)	0.537
Significant RCA stenosis	4017 (86.9%)	1030 (78.5%)	<0.001
Significant LCX stenosis	3796 (82.1%)	848 (64.6%)	<0.001
Discontinuation of antiplatelet drugs Occurring less than 5 days before surgery	2216 (47.9%)	676 (51.5%)	0.022
Preoperative therapy with anticoagulant drugs (vitamin K antagonists)	9 (0.2%)	10 (0.8%)	0.003

COPD: Chronic obstructive pulmonary disease; EF: ejection fraction; IABP: intra-aortic balloon counterpulsation; LAD: left anterior descending coronary artery system; LCX: circumflex artery system; LMT: left main trunk; MI: myocardial infarction; NYHA: New York Heart Association; RCA: right coronary artery system.

account for institutional learning curve), and for patients receiving complete or incomplete revascularization.

A *p* value less than 0.05 was considered significant.

3. Results

3.1. Whole patient population

Preoperative clinical features of the whole patient population are reported in Table 1, whereas intraoperative and postoperative events are displayed in Table 2.

Table 2
Comparison of intraoperative and postoperative events in the whole patient population

	On-pump (n = 4623)	Off-pump (n = 1312)	p-Value
LIMA use	4554 (98.5%)	1252 (95.4%)	<0.001
RIMA use	331 (7.2%)	56 (4.3%)	<0.001
Radial artery use	354 (7.7%)	150 (11.4%)	<0.001
No. of distal anastomoses	3.1 ± 0.86	2.1 ± 0.82	<0.001
Complete revascularization	4091 (88.5%)	858 (65.4%)	<0.001
No. of distals with arterial grafts	1.2 ± 0.42	1.1 ± 0.42	0.003
In-hospital mortality	30 (0.6%)	12 (0.9%)	0.311
Perioperative myocardial infarction	146 (3.2%)	22 (1.7%)	0.004
Perioperative stroke	43 (0.9%)	7 (0.5%)	0.165
Perioperative atrial fibrillation	475 (10.3%)	136 (10.4%)	0.924
Reoperation for bleeding	225 (4.9%)	27 (2.1%)	<0.001
Mechanical ventilation time (h)	12 ± 20.2	8 ± 7.4	<0.001
No. of units of red blood cells (units)	1.2 ± 2.18	0.6 ± 1.39	<0.001

LIMA: left internal mammary artery; RIMA: right internal mammary artery.

3.2. Propensity matched pairs

Factors associated with propensity to use on- and off-pump techniques are reported in Table 3. Preoperative characteristics of on- and off-pump propensity matched patients were well matched (Table 4), including similar extent of coronary artery disease (2.5 ± 0.57 diseased coronary vessels in CABG vs 2.5 ± 0.66 in OPCAB, $p = 0.64$), similar involvement of the left main and of the three major coronary vessels. About intra- and postoperative features (Table 5), matched patients who underwent off-pump surgery had lower rates of left internal mammary artery utilization, whereas the radial

Table 3
Factors associated with propensity to use on- and off-pump techniques

	p-Value
On-pump variable	
Increasing no of diseased vessels	<0.0001
Urgent/emergent surgery	<0.0001
LCX stenosis	0.0001
Off-pump variable	
More recent year of surgery	<0.0001
Redo-operation	<0.0001
Increasing preoperative Tuman score	0.0001
Higher creatinine	0.0002
Old age	0.0003
RCA stenosis	0.0019
Previous stroke	0.0094
Chronic obstructive pulmonary disease	0.0100
Carotid artery disease	0.0127

RCA, right coronary artery system; LCX, left circumflex artery system.

artery was used more frequently. Despite having a similar extent of coronary artery disease, the number of distal anastomoses was lower in patients undergoing OPCAB (2.2 ± 0.80 in OPCAB vs 2.9 ± 0.86 in CABG, $p < 0.001$), as well as complete revascularization rate (61.9% in OPCAB vs 90.0% in CABG, $p < 0.001$). Incomplete revascularization was evenly distributed between lateral (56/106 patients, 52.8%) and inferior (50/106 patients, 47.2%) walls of the heart in patients who underwent on-pump coronary bypass surgery, whereas it was more frequent in the lateral wall (282/405

patients, 69.6%) than in the inferior one (123/405 patients, 30.4%) in patients who were operated off-pump ($p = 0.002$). Major postoperative complications (in-hospital death, stroke, and myocardial infarction) were similar in the on- and off-pump patients. However, off-pump patients experienced less reoperation for bleeding, red blood cell use, and lower times on ventilator.

3.3. Risk factors for perioperative myocardial infarction

Perioperative myocardial infarction occurred in 23 (2.2%) and in 17 (1.6%) propensity-matched patients who underwent CABG and OPCAB, respectively ($p = 0.338$). Table 6 reports the data about severity and location (grafted vs nongrafted territory) of perioperative myocardial infarctions in propensity-matched patients; there were no significant differences in patient undergoing CABG and OPCAB, although it should be noted a slight trend towards higher need of inotropes in patient undergoing CABG and who had a perioperative myocardial infarction (43.5% vs 29.4% in CABG and OPCAB, respectively, $p = 0.364$).

The factors significantly ($p < 0.05$) or possibly ($p < 0.2$) influencing the occurrence of perioperative myocardial infarction at univariate logistic regression analysis performed on the whole patient population are listed in Table 7. Multivariate logistic regression analysis (Table 7) showed that independent predictors of myocardial infarction were, in order of statistical significance year of surgery ($p = 0.0000$,

Table 4
Comparison of patient characteristics in propensity-matched pairs

	On-pump (n = 1062)	Off-pump (n = 1062)	p-Value
Propensity score	-1.093506 ± 0.731642	-1.096061 ± 0.727512	0.936
Age (years)	66 ± 8.0	66 ± 9.5	0.439
Male gender	879 (82.8%)	863 (81.3%)	0.366
Weight (kg)	75 ± 11.4	74 ± 11.9	0.118
Body surface area (m ²)	1.82 ± 0.17	1.81 ± 0.16	0.214
Urgent/emergent surgery	19 (1.8%)	25 (2.4%)	0.361
Hypertension	682 (64.2%)	662 (62.3%)	0.368
Diabetes	256 (24.2%)	224 (20.6%)	0.092
Redo-operation	40 (3.8%)	50 (4.7%)	0.281
Previous stroke	31 (2.9%)	35 (3.3%)	0.617
Carotid artery disease	92 (8.7%)	94 (8.9%)	0.878
Smoke	412 (38.8%)	399 (37.6%)	0.562
COPD	126 (11.9%)	126 (11.9%)	>0.99
Previous MI	431 (40.6%)	438 (41.2%)	0.757
Previous MI, less than 6 months	148 (13.9%)	139 (13.1%)	0.568
Atrial fibrillation	20 (1.9%)	17 (1.6%)	0.619
Dialysis	5 (0.5%)	8 (0.8%)	0.404
Preoperative IABP	6 (0.6%)	2 (0.2%)	0.288
NYHA functional class	2.0 ± 0.66	2.1 ± 0.67	0.425
Echocardiographic EF (%)	56 ± 11.3	57 ± 11.0	0.344
Serum creatinine (mg/dl)	1.1 ± 0.58	1.1 ± 0.51	0.624
Tuman score	2.1 ± 1.8	2.1 ± 1.8	0.452
No. of diseased vessels	2.5 ± 0.57	2.5 ± 0.66	0.648
Significant LMT stenosis	231 (21.8%)	206 (19.4%)	0.180
Significant LAD stenosis	946 (89.2%)	952 (90.3%)	0.414
Significant RCA stenosis	863 (81.3%)	863 (81.3%)	>0.99
Significant LCX stenosis	778 (73.3%)	769 (72.4%)	0.661
Discontinuation of antiplatelet drugs	555 (52.3%)	543 (51.0%)	0.572
Occurring less than 5 days before surgery			
Preoperative therapy with anticoagulant	2 (0.2%)	3 (0.3%)	>0.99
Drugs (vitamin K antagonists)			

COPD: chronic obstructive pulmonary disease; EF: ejection fraction; IABP: intra-aortic balloon counterpulsation; LAD: left anterior descending coronary artery system; LCX: circumflex artery system; LMT: left main trunk; MI: myocardial infarction; NYHA: New York Heart Association; RCA: right coronary artery system.

Table 5
Comparison of intraoperative and postoperative events in propensity-matched pairs

	On-pump (n = 1062)	Off-pump (n = 1062)	p-Value
LIMA use	999 (97.4%)	969 (95.7%)	0.035
RIMA use	66 (6.2%)	52 (4.9%)	0.185
Radial artery use	74 (7.0%)	123 (11.6%)	<0.001
No. of distal anastomoses	2.9 ± 0.86	2.2 ± 0.80	<0.001
Complete revascularization	956 (90.0%)	657 (61.9%)	<0.001
No. of distals with arterial grafts	1.1 ± 0.38	1.1 ± 0.43	0.551
In-hospital mortality	9 (0.8%)	7 (0.7%)	0.616
Perioperative myocardial infarction	23 (2.2%)	17 (1.6%)	0.338
Perioperative stroke	11 (1.0%)	7 (0.7%)	0.344
Perioperative atrial fibrillation	109 (10.3%)	112 (10.5%)	0.831
Reoperation for bleeding	48 (4.5%)	23 (2.2%)	0.003
Mechanical ventilation time (h)	11 ± 13.6	7 ± 5.6	<0.001
No of units of red blood cells (units)	1.2 ± 2.59	0.6 ± 1.44	<0.001

LIMA: left internal mammary artery; RIMA = right internal mammary artery.

being more recent years associated to lower risk), incomplete revascularization ($p = 0.0018$), urgent/emergent surgery ($p = 0.0048$), redo-operation ($p = 0.0249$), the number of distal anastomoses performed ($p = 0.0260$, being higher numbers of distals associated to an increased risk of myocardial infarction), and smoking habitus at the time of surgery ($p = 0.0438$). When multivariate logistic regression analysis was performed only on patients who had complete myocardial revascularization ($n = 4949$, Table 7), the only significant risk factors were the year of surgery ($p = 0.0000$) and the number of distal anastomoses ($p = 0.0227$). In this case it is interesting to note that, even when controlling for completeness of revascularization, increasing number of distal anastomoses were still associated to an increased risk of significant perioperative myocardial infarction. In addition, both incomplete revascularization and increasing number of distals were retained in logistic regression models performed on more recent years of surgical experience (1999–2004 and 2000–2004, Table 7), in order to account for institutional learning curve. Finally, in patients who received incomplete revascularization ($n = 986$, Table 7), the independent risk factors were year of surgery ($p = 0.0014$), urgent/emergent surgery ($p = 0.0170$), and redo-operation ($p = 0.0217$).

4. Discussion

Several studies have reported that standard on-pump coronary artery bypass surgery continues to show favorable short- and long-term outcomes [9]. Nevertheless, due to an increasingly high-risk population, on-pump CABG is still associated with substantial morbidity, which is for the most

part ascribed by some authors [10], but not by all [11], to the adverse effects of extracorporeal circulation.

Over the past years, OPCAB has been explored as an emerging technique for coronary revascularization that might reduce the potentially adverse effects of cardiopulmonary bypass, and the number of procedures performed off-pump has increased significantly. Nevertheless, definitive conclusions about the relative merits of standard CABG and OPCAB are difficult to be reached, as adequate results may be achieved with either type of procedure, and differences, if any, in major perioperative outcomes between the two techniques are so small that very large trials are needed to find possible differences [2,12,13].

In addition, previous studies have shown a lower completeness of revascularization when comparing OPCAB with conventional CABG [3,4]. Incomplete revascularization is known to negatively influence several outcomes after coronary bypass grafting [8,14], and is a risk factor for myocardial damage [15], which leads, in turn, to worse results at follow-up [16].

To the best of our knowledge, there are no reports or comparative studies that address the relations between surgical technique (CABG vs OPCAB), completeness of revascularization and perioperative myocardial infarction.

Our study shows that, similarly to other hard outcomes such as in-hospital mortality and perioperative stroke, once patient clinical features are adjusted for risk, the type of surgical technique (on-pump vs off-pump) does not affect perioperative myocardial infarction rates, being very similar in propensity-matched pairs (2.2% in CABG vs 1.6% in OPCAB, respectively). This is in line with previous studies that failed to document any significant difference in terms of perioperative myocardial infarction or other hard outcomes between CABG and OPCAB [3,5,13]; moreover, it confirms and extends evidence coming from several studies performed with different designs (meta-analyses, randomized and nonrandomized risk-adjusted studies) that show no difference between the OPCAB and standard CABG procedures, even if some advantage can be achieved in term of minor complications with the adoption of the off-pump technique.

Multivariate analysis also confirms that the choice of on- or off-pump surgery does not significantly affect the occurrence of clinically significant perioperative myocardial infarction. Interestingly, in addition to variables indicating

Table 6
Perioperative myocardial infarction features in propensity-matched pairs

	On-pump (n = 23)	Off-pump (n = 17)	p-Value
MI location in a grafted territory	18 (78.3%)	12 (70.6%)	0.717
Postoperative inotropes	10 (43.5%)	5 (29.4%)	0.364
Postoperative IABP	7 (30.4%)	3 (25.0%)	0.471
Postoperative ECMO	1 (4.3%)	1 (5.9%)	>0.99
In-hospital mortality	1 (4.3%)	1 (5.9%)	>0.99

ECMO: extra-corporeal membrane oxygenation; IABP: intra-aortic balloon counterpulsation; MI: myocardial infarction.

Table 7
Univariate and multivariate analysis of factors influencing perioperative myocardial infarction

Variable	Univariate logistic regression analysis		Multivariate logistic regression analysis		Multivariate logistic regression analysis		Multivariate logistic regression analysis		Multivariate logistic regression analysis	
	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)
CABG (on-pump bypass surgery)	0.1747	1.45 (0.85–2.48)	–	–	–	–	–	–	–	–
Calendar year	0.0000	0.79 (0.73–0.85)	0.0000	0.80 (0.75–0.85)	0.0000	0.79 (0.73–0.85)	0.0014	0.81 (0.71–0.92)	–	–
Urgent/emergent surgery	0.0801	2.0 (0.9–4.3)	0.0048	2.6 (1.3–5.2)	–	–	0.0170	4.9 (1.3–18.2)	0.0350	0.83 (0.69–0.99)
Redo-operation	0.0335	2.1 (1.1–4.0)	0.0249	2.1 (1.1–4.0)	–	–	0.0217	3.0 (1.2–7.7)	–	–
Current smoker	0.0156	1.52 (1.08–2.14)	0.0438	1.41 (1.01–1.97)	–	–	–	–	–	–
Tuman score	0.1994	1.06 (0.97–1.17)	–	–	–	–	–	–	–	–
Discontinuation of antiplatelet drugs occurring less than 5 days before surgery	0.0827	1.77 (0.93–3.36)	–	–	–	–	–	–	–	–
No. of distal anastomoses	0.0923	1.25 (0.96–1.61)	0.0260	1.26 (1.03–1.54)	0.0227	1.27 (1.03–1.57)	–	–	0.0094	1.76 (1.15–2.70)
No. of distals with arterial grafts	0.1530	0.67 (0.39–1.16)	–	–	–	–	–	–	–	–
LIMA use	0.1828	0.67 (0.37–1.21)	–	–	–	–	–	–	0.0173	0.26 (0.08–0.79)
Complete revascularization	0.0059	0.44 (0.24–0.79)	0.0018	0.45 (0.28–0.74)	–	–	–	–	0.0015	0.24 (0.09–0.58)
Hosmer and Lemeshow goodness-of-fit test	0.2870	–	0.7478	–	0.7208	–	0.9739	–	0.8119	0.8149

that high complexity or high risk procedures (e.g. operation on an urgent/emergent basis and redo-operations) or improvement of patient management over time (year of surgery) influence this complication, two apparently opposite factors related to the extent of revascularization achieved with the operation emerge at multivariate analysis as risk factors for perioperative myocardial infarction: incomplete revascularization and increasing number of distal anastomoses performed. It is also important to note that the number of distal anastomoses is retained as a significant risk factor for perioperative myocardial infarction both in the model considering the whole patient population and in the model analyzing only patients classified as having complete revascularization at intervention, controlling for completeness of revascularization.

The achievement of complete revascularization is one of the main goals of coronary bypass surgery whatever the technique chosen, as incomplete revascularization may adversely affect not only the early, but also the late results [17,18]. Our study shows that the incomplete revascularization rates are not irrelevant both for CABG and OPCAB, and are higher when the OPCAB strategy is adopted. The incomplete revascularization rates reported in our study are in line with previous experiences [3,4] and, although it was not possible to know exactly the reason for each case, they can be explained by technical and strategical reasons. Regarding technical causes, it is possible that the non-use of apical suction stabilizers, that make revascularization of the lateral and inferior wall of the heart less technically demanding, which instead have become available in the very late part of our experience, might have contributed to a less complete revascularization. In addition, strategical issues might have played an important role as determinants of incomplete revascularization: and some of these can be related to the risk profile of the patient (e.g. when the surgeon may feel that a quicker, less extensive surgery may be better tolerated by a sick patient), whereas others can be related to the quality of the coronary vessels that need to be grafted which, sometimes, may be discouraging because of the calliper or because of the presence of diffuse disease. All these possible causes are obviously more relevant in OPCAB that is per se a more technical demanding strategy, and for this reason, although some experienced OPCAB surgeons have demonstrated the ability to achieve 100% complete revascularization in OPCAB patients [19], most series show a near doubling of incomplete revascularization in OPCAB setting [3,4,18]. In addition, the features of our study, retrospective and 'on the road', totally represent our practice over a 10-year period of time. This implies that patients were not selected a priori in any way, and the only criterion for patients to be included in the study was the absence of concomitant procedures. And this is really different from prospective randomized trials where it is easier to achieve higher complete revascularization rates due to some sort of a priori selection of the patients; and this, in our opinion, makes randomized studies sometimes less representative of the patient population undergoing coronary bypass surgery.

The prominent role of OPCAB in the occurrence of incomplete revascularization has then been confirmed by

Table 8
Univariate and multivariate analysis of factors influencing incomplete revascularization

Variable	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	All patients (n = 5935)		All patients (n = 5935)	
	p-Value	OR (95% CI)	p-Value	OR (95% CI)
OPCAB (off-pump bypass surgery)	0.0000	6.7 (5.6–8.3)	0.0000	7.1 (5.9–8.3)
Age	0.0450	1.01 (1.00–1.02)	0.0258	1.01 (1.00–1.02)
Calendar year	0.0646	0.97 (0.93–1.00)	0.0077	0.96 (0.93–0.99)
Redo-operation	0.0005	1.97 (1.34–2.90)	0.0006	1.95 (1.33–2.86)
COPD	0.1977	1.19 (0.91–1.55)	–	–
Atrial fibrillation	0.0493	1.72 (1.00–2.94)	0.0429	1.74 (1.02–2.97)
Echocardiographic EF	0.0622	0.99 (0.98–1.00)	0.0161	0.99 (0.98–1.00)
Serum creatinine	0.1591	1.12 (0.96–1.30)	–	–
Tuman score	0.0084	1.07 (1.02–1.13)	0.0008	1.09 (1.04–1.15)
No of diseased vessels	0.0000	7.6 (5.8–10.0)	0.0000	7.7 (5.9–10.0)
Significant RCA stenosis	0.0000	0.51 (0.38–0.70)	0.0000	0.52 (0.38–0.70)
Hosmer and Lemeshow goodness-of-fit test	0.1525		0.1875	–

additional multivariate analyses performed on our patient population showing that OPCAB technique was the most significant predictor (OR 7.1, 95% CI 5.9–8.3, $p = 0.0000$) of incomplete revascularization (Table 8); of note, no interaction was detected between surgical strategy (CABG vs OPCAB) and incomplete revascularization as predictors of perioperative myocardial infarction. Finally, the issue of higher incomplete revascularization rates in OPCAB, together with the warnings of reduced patency of the bypasses done off-pump [20], supports the emerging evidence of reduced freedom from revascularization at follow-up for patients undergoing off-pump coronary bypass surgery [21], although the relative contribution of each of these potential causes still needs to be determined.

In our study, a higher number of distal anastomoses seem to be associated to greater perioperative myocardial infarction rates. This suggests that a too aggressive revascularization strategy, with more than one distal anastomosis done per ischemic territory (left anterior descending, circumflex, and right coronary artery systems) is detrimental for the patient. This observation confirms and extends previous evidence from the re-analysis of the data of BARI trial, which documented that overgrafting patients in the non LAD-dependent territory increases the risk of death/myocardial infarction at follow-up [22]. Data from our study show that the increased risk for myocardial infarction due to overgrafting occurs also in the early perioperative period. An increased stress posed to the heart due to longer procedures, the possible accumulation of technical faults due to an increased number of anastomoses, or flow competition that can occur especially in case of borderline coronary stenoses may well explain these findings.

Further prospective randomized studies aimed at exploring the mechanisms and potential risks of overgrafting patients either in on- or in off-pump coronary bypass surgery are still needed to confirm these hypotheses.

Taken together, these data suggest that surgical strategies leading to incomplete or too extensive revascularization are both potentially detrimental and may increase the occurrence of postoperative myocardial infarction. Moreover, one can envision that the choice of an on- or off-pump approach for coronary revascularization should take into account the chances of over- or undergrafting the patient, respectively.

5. Study limitations

This study was a retrospective study of patients who underwent CABG and OPCAB. Patients were not randomly assigned to either group, but instead the choice of procedure was made by the surgeon at the time of operation. Therefore, selection bias may affect our findings. To reduce the effect of selection bias on outcomes, we used propensity matching to identify well-matched off-pump and on-pump patients for comparison (off-pump and on-pump groups were well matched in all evaluated preoperative characteristics), and multivariate logistic regression analysis to simultaneously correct for differences in baseline clinical variables.

The finding that more than one graft to every coronary system is associated with higher perioperative myocardial infarction rates can be alternatively explained by the fact that an increasing number of distal anastomoses can be a marker for more extensive coronary disease that might have contributed to the increased infarction rates. However, the number of coronary systems involved was included as covariate in all logistic regression models and was not associated with the occurrence of perioperative myocardial infarction. Another alternative explanation is that an increasing number of distal anastomoses can be a surrogate marker for increasing cross-clamp and cardiopulmonary bypass times which are known risk factors for perioperative myocardial damage. The effect of increasing cross-clamp and cardiopulmonary bypass times was studied in separate logistic regression models considering only patients undergoing on-pump coronary surgery, and both variables were not retained in the final model, whereas an increasing number of distals was retained as a significant risk factor for perioperative myocardial infarction (data not shown).

The method that was chosen to define and ascertain the occurrence of perioperative myocardial infarction, even if widely accepted in clinical practice, does not eliminate the chance of lesser myocardial damage in terms of enzyme/myocardial protein release as previously described for patients undergoing OPCAB [2,3]. The analysis of our experience covered ten years of surgical practice, and even if during this time period several new markers of myocardial damage have emerged with potential application in a clinical setting, they were not validated at the beginning of the time

period of the study, and they could not be for this reason taken into account.

Acknowledgement

This study was performed at Centro Cardiologico Monzino I.R.C.C.S., University of Milan.

References

- [1] Lytle BW, Sabik JF. On-pump and off-pump bypass surgery: tools for revascularization. *Circulation* 2004;109:810–2.
- [2] Sellke FW, DiMaio JM, Caplan LR, Ferguson TB, Gardner TJ, Hiratzka LF, Isselbacher EM, Lytle BW, Mack MJ, Murkin JM, Robbins RC, American Heart Association. Comparing on-pump and off-pump coronary artery bypass grafting: numerous studies but few conclusions: a scientific statement from the American Heart Association council on cardiovascular surgery and anesthesia in collaboration with the interdisciplinary working group on quality of care and outcomes research. *Circulation* 2005;111:2858–64.
- [3] Sabik JF, Gillinov AM, Blackstone EH, Vacha C, Houghtaling PL, Navia J, Smedira NG, McCarthy PM, Cosgrove DM, Lytle BW. Does off-pump coronary surgery reduce morbidity and mortality? *J Thorac Cardiovasc Surg* 2002;124:698–707.
- [4] Widimsky P, Straka Z, Stros P, Jirasek K, Dvorak J, Votava J, Lisa L, Budesinsky T, Kolesar M, Vanek T, Brucek P. One-year coronary bypass graft patency: A randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. *Circulation* 2004;110:3418–23.
- [5] Cheng DC, Bainbridge D, Martin JE, Novick RJ. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *Anesthesiology* 2005;102:188–203.
- [6] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.
- [7] Jain U. Myocardial infarction during coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 1992;6:612–3.
- [8] Jones EL, Weintraub WS. The importance of completeness of revascularization during long-term follow-up after coronary artery operations. *J Thorac Cardiovasc Surg* 1996;112:227–37.
- [9] Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, Schonberger JP, Buller N, Bonser R, Disco C, Backx B, Hugenholtz PG, Firth BG, Unger F. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol* 2005;46:575–81.
- [10] Buffolo E, Branco JN, Gerola LR, Aguiar LF, Teles CA, Palma JH, Catani R. Off-pump myocardial revascularization: critical analysis of 23 years' experience in 3,866 patients. *Ann Thorac Surg* 2006;81:85–9.
- [11] Biglioli P, Cannata A, Alamanni F, Naliato M, Porqueddu M, Zanobini M, Tremoli E, Parolari A. Biological effects of off-pump versus on-pump coronary artery surgery: focus on inflammation, hemostasis and oxidative stress. *Eur J Cardiothorac Surg* 2003;24:260–9.
- [12] Parolari A, Alamanni F, Cannata A, Naliato M, Bonati L, Rubini P, Veglia F, Tremoli E, Biglioli P. Off-pump versus on-pump coronary artery bypass: meta-analysis of currently available randomized trials. *Ann Thorac Surg* 2003;76:37–40.
- [13] Wijesundera DN, Beattie WS, Djaiani G, Rao V, Borger MA, Karkouti K, Cusimano RJ. Off-pump coronary artery surgery for reducing mortality and morbidity: meta-analysis of randomized and observational studies. *J Am Coll Cardiol* 2005;46:872–82.
- [14] Scott R, Blackstone EH, McCarthy PM, Lytle BW, Loop FD, White JA, Cosgrove DM. Isolated bypass grafting of the left internal thoracic artery to the left anterior descending coronary artery: late consequences of incomplete revascularization. *J Thorac Cardiovasc Surg* 2000;120:173–84.
- [15] Onorati F, De Feo M, Mastroberoberto P, Cristodoro L, Pezzo F, Renzulli A, Cotrufo M. Determinants and prognosis of myocardial damage after coronary artery bypass grafting. *Ann Thorac Surg* 2005;79:837–45.
- [16] Stenotic atherosclerotic coronary artery disease. In: Kouchoukos NT, Blackstone EH, Doty DB, Hanley FL, Karp RB, editors. *Kirklin/Barrat-Boyes cardiac surgery*. 3rd ed. Philadelphia: Churchill Livingstone; 2003:353–436.
- [17] Bell MR, Gersh BJ, Schaff HV, Holmes Jr DR, Fischer LD, Alderman EL, Myers WO, Parsons LS, Reeder GS. Effect of completeness of revascularization on long-term outcome of patients with three-vessel disease undergoing coronary artery bypass surgery: a report from the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1992;86:446–57.
- [18] Kleisli T, Cheng W, Jacobs MJ, Mirocha J, DeRobertis MA, Kass RM, Blanche C, Fontana GP, Raissi SS, Magliato KE, Trento A. In the current era, complete revascularization improves survival after coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2005;129:1283–91.
- [19] Puskas JD, Williams WH, Mahoney EM, Huber PR, Block PC, Duke PG, Staples JR, Glas KE, Marshall JJ, Leimbach ME, McCall SA, Petersen RJ, Bailey DE, Weintraub WS, Guyton RA. Off-pump versus conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes – a randomized trial. *JAMA* 2004;291:1841–9.
- [20] Parolari A, Alamanni F, Polvani G, Agrifoglio M, Chen YB, Kassem S, Veglia F, Tremoli E, Biglioli P. Meta-analysis of randomized trials comparing off-pump with on-pump coronary artery bypass graft patency. *Ann Thorac Surg* 2005;80:2121–5.
- [21] Hannan EL, Wu C, Smith CR, Higgins RS, Carlson RE, Culliford AT, Gold JP, Jones RH. Off-pump versus on-pump coronary artery bypass graft surgery: differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. *Circulation* 2007;116:1145–52.
- [22] Vander Salm TJ, Kip KE, Jones RH, Shaff HV, Shemin RJ, Aldea GS, Detre KM. What constitutes optimal surgical revascularization? Answers from the bypass angioplasty revascularization investigation (BARI) *J Am Coll Cardiol* 2002;39:565–72.

Appendix A. Monzino OPCAB Investigators

Matteo Trezzi MD, Claudia Loardi MD, Samer Kassem MD, Massimo Porqueddu MD PhD, Maurizio Roberto MD PhD, Marco Zanobini MD PhD, Luca Salvi MD, Melissa Fusari MD, Stefano Salis MD, Fabrizio Veglia PhD, Erminio Sisillo MD, Elena Tremoli PhD.

Appendix B

See Table B.1.

Table B.1
Patient variables considered in analyses

Preoperative	
1. Age (years)	
2. Gender (m/f)	
3. Weight (kg)	
4. Body surface area (m ²)	
5. Year of surgery (1995–2004)	
6. Urgent/emergent surgery (y/n)	
7. Hypertension (y/n)	
8. Diabetes (insulin treated, oral hypoglycemic (y/n)	
9. Redo-operation (y/n)	
10. Previous stroke (y/n)	
11. Carotid artery disease (y/n)	
12. Current smoker (y/n)	
13. Chronic obstructive pulmonary disease (y/n)	
14. Previous myocardial infarction (y/n)	
15. Previous myocardial infarction, less than 6 months (y/n)	
16. Atrial fibrillation (y/n)	
17. Dialysis (y/n)	
18. Preoperative intra-aortic balloon counterpulsation (y/n)	
19. NYHA functional class (1–4)	
20. Echocardiographic ejection fraction (%)	
21. Serum creatinine (mg/dl)	
22. Tuman score	
23. No. of diseased vessels (1–3)	
24. Significant (>50%) stenosis in left main trunk (y/n)	

25. Significant (>50%) stenosis in left anterior descending coronary artery system (y/n)
26. Significant (>50%) stenosis in right coronary artery system (y/n)
27. Significant (>50%) stenosis in circumflex artery system (y/n)
28. Discontinuation of antiplatelet drugs occurring less than 5 days before surgery (y/n)
29. Preoperative therapy with anticoagulant drugs (vitamin K antagonists) (y/n)

Intraoperative

30. LIMA use (y/n)
31. RIMA use (y/n)
32. Radial artery use (y/n)
33. No. of distal anastomoses
34. Complete revascularization (y/n)
35. No. of distals with arterial grafts

Postoperative

36. In-hospital mortality (y/n)
 37. Perioperative myocardial infarction (y/n)
 38. Perioperative stroke (y/n)
 39. Perioperative atrial fibrillation (y/n)
 40. Reoperation for bleeding (y/n)
 41. Mechanical ventilation time (h)
 42. No. of units of red blood cells (units)
-