

Randomized Trial Comparing Off-Pump to On-Pump Coronary Artery Bypass Grafting in High-Risk Patients

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ABSTRACT

Objective: The subset of patients most likely to benefit from off-pump coronary artery bypass grafting (CABG) remains a controversial issue, but the technique has been proposed to decrease postoperative mortality and morbidity. The objective of this study was to compare off-pump to on-pump CABG in patients with known risk factors for mortality and morbidity.

Methods: Between October 2001 and September 2002, 65 high-risk patients were prospectively randomized to undergo off-pump or on-pump CABG. Recruited patients had at least 3 of the following criteria: age greater than 65 years, high blood pressure, diabetes, serum creatinine greater than 133 $\mu\text{mol/L}$, left ventricular ejection fraction lower than 45%, chronic pulmonary disease, unstable angina, congestive heart failure, repeat CABG, anemia, and carotid atherosclerosis. Hospital mortality and morbidity were the primary end-points of the study.

Results: Six patients (9%) crossed over from the original randomized group. Twenty-eight patients averaging 70 ± 8 years of age underwent 3 ± 1 grafts off pump, and 37 patients averaging 70 ± 6 years of age underwent 3.4 ± 1 grafts on pump. Revascularization was considered complete in 21 (75%) of off-pump patients compared to 33 (89%) of on-pump patients ($P = .1$). There were no hospital deaths in off-pump patients, and 2 patients (5%) undergoing on-pump CABG died early following surgery ($P = .2$). Two off-pump (7%) compared to 11 on-pump (30%) of patients presented composite end-points including death, neurological injury, renal failure, respiratory failure, and operative myocardial infarction after CABG ($P = .02$).

Conclusion: The present study suggests that off-pump CABG, when technically feasible, significantly reduces morbidity following surgery in a group of high-risk patients.

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INTRODUCTION

Coronary artery bypass grafting (CABG) is currently performed with or without the use of the cardiopulmonary bypass system (CPB). Although both techniques are being used with success [Van Dijk 2001], a debate is raging between advocates and opponents of off-pump CABG about patient outcomes and surgical indications for one or the other technique [Bonchek 2002].

Several authors have suggested that off-pump CABG could be especially useful and effective in improving clinical outcomes in high-risk patients who require surgical revascularization [Hoff 2002, Al-Ruzzeh 2003]. Elderly patients and those with significant comorbidities are more susceptible to the deleterious effects of CPB and are most likely to benefit from the use of off-pump CABG compared to the standard on-pump approach [Demaria 2002].

The objective of the present study was to compare outcomes between off-pump CABG and a standard technique of CABG with CPB and cardioplegic arrest in a group of patients at high risk of postoperative mortality and morbidity.

METHODS

Study Population

Between October 2001 and September 2002, 65 patients undergoing CABG at the Montreal Heart Institute were prospectively randomized into 2 groups: one undergoing off-pump CABG and the other undergoing standard on-pump CABG. After the patients had agreed to participate in the study, fulfilled inclusion criteria, and signed an informed consent form, they were randomized in the operating room just before the beginning of the operation. Randomization by blocks of 4 was used to obtain equal sample size in the 2 groups.

Recruited patients had at least 3 of the following criteria: age greater than 65 years, high blood pressure, diabetes, serum creatinine greater than 133 $\mu\text{mol/L}$, left ventricular ejection fraction lower than 45%, chronic pulmonary disease, unstable angina, congestive heart failure, repeat CABG, anemia, and significant carotid atherosclerosis. In our database, patients with at least 3 of the above criteria had a risk of combined hospital mortality and of significant morbidity averaging 30%. The study sample size was chosen to show a decrease of 30% of the following combined end-points (with an alpha error of 5% and a power of 80%): hospital mortality,

Table 1. Clinical Characteristics of Patients*

	Off-Pump Group	On-Pump Group	P
No. of patients	28	37	
Age, y	70 ± 8	70 ± 6	.8
Women/men	9/19	6/31	.1
Stable/unstable angina	7/21	15/22	.2
Left main stenosis	8 (29%)	12 (32%)	.7
Three-vessel disease	18 (64%)	30 (81%)	.1
LV dysfunction	4 (6%)	9 (14%)	.3
Creatinine >133 μmol/L	2 (7%)	4 (11%)	.7
High blood pressure	23 (82%)	30 (81%)	.7
COPD	7 (25%)	8 (22%)	.7
Congestive heart failure	2 (7%)	5 (14%)	.4
Diabetes	14 (50%)	17 (46%)	.7
Anemia (Hb <12 gm/L)	9 (32%)	6 (16%)	.1
Carotid disease	6 (21%)	7 (19%)	.8

*LV dysfunction indicates left ventricular ejection fraction <45%; COPD, chronic obstructive pulmonary disease.

postoperative myocardial infarction defined with serial CK-MB (creatinine kinase isoenzyme MB) levels greater than 100 units or a new Q wave on postoperative electrocardiogram, stroke or transient neurological deficit, renal insufficiency with dialysis or with an increase of 100 μmol/L from baseline serum creatinine, and respiratory failure or infection requiring prolonged mechanical ventilation.

The study was approved and monitored by the Ethics Committee of the Research Center of the Montreal Heart Institute.

Surgical Technique

Perioperative management was standardized in the two groups. All operations were performed through a standard median sternotomy. Off-pump CABG was performed with the use of commercially available myocardial stabilizers and previously reported surgical techniques [Cartier 1999, Dagenais 1999, Perrault 2000]. On-pump CABG was performed according to standard surgical techniques with CPB (membrane oxygenator) using moderate hemodilution and mild systemic hypothermia averaging 33°C. Blood cardioplegia and aprotinin were used in all patients in the on-pump group [Wong 2000, Carrier 2002].

Surgeons were asked to identify the target coronary vessels the day before surgery, and completeness of revascularization was assessed in comparing the number of preoperative planned coronary grafts to the number of grafts performed per patient.

Data Analysis

Analysis of continuous variables was performed with the Student *t* test, and the chi-square or the Fisher exact test was used for the comparison of discontinuous data. Data analysis was performed with the Number Cruncher Statistical System 2001 (NCSS Statistical Software, Kaysville, UT, USA).

RESULTS

Preoperative Profiles of Patients

Among the 65 randomized patients, 32 were assigned to the off-pump CABG and 33 to the on-pump CABG group. Six patients (9%) crossed over from the original randomized group: 5 patients assigned to the off-pump group underwent CABG with the standard method using CPB, and 1 patient assigned to the on-pump group underwent CABG with the off-pump approach. Although patient recruitment and informed consent were obtained by 3 research assistants, the final decision of feasibility was left to the attending surgeon in the operating room. Thus, 28 patients underwent CABG without the use of a CPB system and 37 underwent CABG with CPB at one point in time during the operation.

The 2 groups of patients had similar preoperative clinical characteristics (Table 1). Patients averaged 70 years of age in both groups and most had significant triple-vessel disease or a left main stenosis. Renal dysfunction defined with preoperative serum creatinine higher than 133 μmol/L was similar in both groups.

Surgical Procedures

All patients had an internal mammary artery grafted to the left anterior descending coronary artery and complementary saphenous vein grafts to the other coronary territories. The number of grafts averaged 3 per patients in the 2 groups, and the revascularization was completed as planned before surgery in 75% of off-pump patients and in 89% of on-pump patients, a nonsignificant difference (Table 2).

Postoperative Morbidity and Mortality

Two patients died of postoperative myocardial infarction, an 85-year-old woman, undergoing redo CABG, who was initially assigned to the off-pump group but converted to CPB because of technical difficulties and a 76-year-old man who was assigned to and underwent on-pump CABG. There were no deaths among patients in the off-pump group who underwent CABG without the use of the CPB system (Table 3).

Two patients (2/28, 7%) undergoing off-pump CABG showed evidence of postoperative renal insufficiency compared to 11 patients (11/37, 30%) with postoperative myocardial infarction, stroke, renal insufficiency, and respiratory failure after undergoing on-pump CABG, a significant difference ($P = .02$) (Table 3).

Blood loss amounts, including operative and postoperative periods, averaged 1172 ± 583 mL in off-pump patients and

Table 2. Operative Data

	Off-Pump Group (n = 28)	On-Pump Group (n = 37)	P
No. grafts per patient	3 ± 1	3.4 ± 1	.1
Complete revascularization	21 (75%)	33 (89%)	.1
Duration of surgery, min	153 ± 35	170 ± 54	.2
Operating room time, min	229 ± 33	240 ± 60	.4

Table 3. Comparison of Postoperative Mortality and Morbidity*

	Off-Pump Group (n = 28)	On-Pump Group (n = 37)	P
Death (30 d)	0	2 (5%)	.2
Composite end-points	2 (7%)	11 (30%)	.02
Myocardial infarction	0	2 (5%)	.2
Stroke/TIA	0	1 (3%)	.4
Renal insufficiency	2 (7%)	5 (14%)	.4
Respiratory failure or infection	0	6 (16%)	.03
Total blood losses, mL	1172 ± 583	796 ± 569	.01
Blood transfusion, units	0.9 ± 1.5	1.4 ± 2	.2
Patients transfused, no.	10 (36%)	18 (49%)	.3
ICU length of stay, d	2 ± 1	3.1 ± 3.6	.1
Hospital stay, d	5.6 ± 3.1	6.7 ± 4.3	.2

*TIA indicates transient ischemic attack or neurological deficit; renal insufficiency, the need for dialysis or an increase of more than 100 mmol/L of the postoperative creatinine value from baseline; composite end-points, death (30 days) or postoperative myocardial infarction, stroke, transient neurological deficit, renal insufficiency, respiratory failure, or infection; total blood losses, intra- and postoperative mediastinal blood losses.

796 ± 569 in on-pump patients, a significant difference ($P = .01$). The number of blood transfusion units administered and the number of patients who were administered blood transfusion after CABG was similar in both groups.

Cross-Over Patients

One patient (1/33, 3%) initially assigned to the on-pump group underwent CABG with the off-pump approach because of the presence of calcification in the ascending aorta. This patient had an uneventful postoperative course. Among the 5 patients (5/32, 16%) initially assigned to the off-pump group who underwent CABG with CPB support, 1 patient died of a massive postoperative myocardial infarction, another patient had a lower respiratory tract infection, and the 3 other patients had uneventful postoperative recovery.

COMMENT

The present study results suggest that high-risk patients who underwent off-pump CABG, when surgeons elected to perform the procedure after surgical assessment in the operating room, had significantly reduced postoperative morbidity compared to high-risk patients who underwent CABG with CPB support. Although the number of patients recruited in the study is small to show clinical benefit, the surgery was performed by 3 surgeons who have several years of experience with both techniques and who agreed to participate in the study. Moreover, the use of a composite end-point including all major complications usually encountered after CABG showed that overall postoperative morbid events were significantly decreased in the group of off-pump patients.

Patient characteristics at baseline were similar, and patient age averaged 70 years in both groups. A preliminary analysis of our database suggested that a combination of our preoper-

ative inclusion criteria would result in an incidence averaging 30% of significant hospital morbidity following CABG using the standard on-pump approach. Using the off-pump technique resulted in a 77% decrease in the incidence of the composite end-points including death, postoperative myocardial infarction, neurological injury, and renal and respiratory insufficiency.

Several authors have suggested, in light of retrospective study results, that off-pump CABG decreases postoperative morbidity following surgery compared with on-pump techniques [Boyd 1999, Hoff 2002, Meharwal 2002, Al-Ruzzeh 2003]. Arom et al [2000] showed that off-pump CABG in high-risk patients resulted in a lower number of grafts per patient, shorter intubation time, lower incidence of renal failure after surgery, and a decrease in hospital mortality compared with on-pump patients. The present study shows a similar decrease in the composite end-point of mortality, myocardial infarction, and neurological, respiratory and renal complications in patients who underwent off-pump CABG. In the latter study and in most experiences reported so far, blood losses were significantly lower with the use of the off-pump technique. In the present study, total blood losses were significantly higher in off-pump patients compared with on-pump patients, but all those subjected to the use of the CPB system received a full course of aprotinin, a very effective protease inhibitor with a powerful effect in decreasing postoperative blood losses.

Sabik et al [2002] and Cheng et al [2002] also reported that off-pump CABG reduces postoperative morbidity at the expense of a more incomplete revascularization. Arom et al [2000] also found that off-pump patients had a higher rate of recurrent angina and reinterventional procedures compared with on-pump patients 1 year after surgery.

We recognize that the present study will not put an end to the current debate raging about the use of the off-pump approach for coronary revascularization [Yacoub 2001, Bonchek 2002, Mack 2002]. Yet, our approach with a prospective randomized study focusing on a group of patients at higher risk of postoperative mortality and morbidity brought out the benefit of the off-pump approach to decrease morbid events after surgery. The elderly patients and those with significant preoperative comorbidities appeared to benefit from the use of off-pump CABG compared with on-pump techniques as long as the surgeon was comfortable with the latter option after a thorough assessment of the difficulties encountered in the operating room. In our study and in our experience, the use of CPB was not considered as a failure but as a necessity to complete the procedure as safely as possible. Five (5/32, 16%) of the patients initially assigned to off-pump CABG underwent myocardial revascularization with the use of a CPB system after thorough assessment of the coronary anatomy and of the technical difficulties.

Thus, the present study supports the off-pump approach in elderly patients and in patients with preoperative comorbidities. Surgical assessment in the operating room should indicate that the technique can be safely used and will result in a near complete myocardial revascularization. Otherwise, on-pump techniques, blood cardioplegic arrest, and a full course of aprotinin should be used.

REFERENCES

- Al-Ruzzeh S, Nakamura K, Athanasiou T, et al. 2003. Does off-pump coronary artery bypass (OPCAB) surgery improve the outcome in high-risk patients? A comparative study of 1398 high-risk patients. *Eur J Cardiothorac Surg* 23:50-5.
- Arom KV, Flavin TF, Emery RW, et al. 2000. Safety and efficacy of off-pump coronary artery bypass grafting. *Ann Thorac Surg* 69:704-10.
- Bonchek LI. 2002. Off-pump coronary bypass: Is it for everyone? *J Thorac Cardiovasc Surg* 124:431-4.
- Boyd WD, Desai ND, Del Rizzo DF, et al. 1999. Off-pump surgery decreases postoperative complications and resource utilization in the elderly. *Ann Thorac Surg* 68:1490-3.
- Carrier M, Pellerin M, Perrault LP, et al. 2002. Cardioplegic arrest with L-arginine improves myocardial protection: results of a prospective randomized clinical trial. *Ann Thorac Surg* 73:837-42.
- Cartier R. 1999. Systematic off-pump coronary artery revascularization: experience of 275 cases. *Ann Thorac Surg* 68:1494-7.
- Cheng W, Denton TA, Fontana GP, et al. 2002. Off-pump coronary surgery: effect on early mortality and stroke. *J Thorac Cardiovasc Surg* 124:313-20.
- Dagenais F, Perrault LP, Cartier R, et al. 1999. Beating heart coronary artery bypass grafting: technical aspects and results in 200 patients. *Can J Cardiol* 15:867-72.
- Demaria RG, Carrier M, Fortier S, et al. 2002. Reduced mortality and strokes with off-pump coronary artery bypass grafting surgery in octogenarians. *Circulation* 106:15-110.
- Hoff SJ, Ball SK, Coltharp WH, et al. 2002. Coronary artery bypass in patients 80 years and over: is off-pump the operation of choice? *Ann Thorac Surg* 74:S1340-3.
- Mack MJ, Duhaylongsod FG. 2002. Through the open door! Where has the ride taken us? *J Thorac Cardiovasc Surg* 124:655-9.
- Meharwal ZS, Mishra YK, Kohli V, et al. 2002. Off-pump multivessel coronary artery surgery in high-risk patients. *Ann Thorac Surg* 74:S1353-7.
- Nathoe HM, Diederik VD, Jansen EW, et al. 2003. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. *N Engl J Med* 348:394-402.
- Perrault LP, Nickner C, Desjardins N, et al. 2000. Effects of coronary endothelial function of the Cohn stabilizer for beating heart bypass operations. *Ann Thorac Surg* 70:1111-4.
- Sabik JF, Gillinov AM, Blackstone EH, et al. 2002. Does off-pump coronary surgery reduce morbidity and mortality? *J Thorac Cardiovasc Surg* 124:698-707.
- Van Dijk D, Nierich AP, Jansen EW, et al. 2001. Early outcomes after off-pump versus on-pump coronary bypass surgery: results from a randomized study. *Circulation* 104:1761-6.
- Wong BI, McLean RF, Fremes SE, et al. 2000. Aprotinin and tranexamic acid for high transfusion risk in cardiac surgery. *Ann Thorac Surg* 69:808-16.
- Yacoub M. 2001. Off-pump coronary bypass surgery. In search of an identity. *Circulation* 104:1743-5.