Off-pump versus on-pump coronary artery bypass: does number of grafts performed represent a selection bias in comparative studies? Results from a matched cohort comparison

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Background. **Several retrospective studies comparing off-pump and on-pump coronary surgery and the largest randomized studies published to date showed a lower number of grafts performed in patients submitted to off-pump coronary artery bypass surgery (OPCAB). These findings bring about the question of the general applicability of the results. We eliminated the selection bias correlated with the number of grafts per patient by comparing the short-term outcomes of patients undergoing OPCAB and standard coronary artery bypass grafting (CABG) matched for number of grafts.**

Methods. **Eighty-seven consecutive patients undergoing OPCAB (group A) were selected from the database of our Institution during a 2-year period. Matching was performed by iterative selection prioritizing, in the following sequence: number of grafts, EuroSCORE, and age. A total of 87 patients operated upon with the on-pump technique represented the control group (group B).**

Results. **There were no significant differences in preoperative characteristics between the two groups. The number of grafts per patient was 2.2 ± 0.5 in group A and 2.2 ± 0.5 in group B. Early mortality did not differ between the two groups and it was 2.2% (2 patients) in group A and 3.4% (3 patients) in group B (p = NS). The incidence of myocardial infarction did not differ between the two groups. No patient in either group had stroke or coma. Five (5.7%) patients in group A and 7 (8.0%) patients in group B had atrial fibrillation (p = NS).**

Conclusions. **We were unable to demonstrate any significant differences in short-term mortality or morbidity outcome between OPCAB and standard CABG patients. Our findings suggest that excellent results can be obtained with both surgical approaches.**

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Introduction

Off-pump coronary artery bypass surgery (OPCAB) has shown good results with low mortality and morbidity in the postoperative period, lower costs, and less use of blood products[1-4]. As a result OPCAB has gained an ever-increasing popularity in the attempt to reduce patient morbidity related to cardiopulmonary bypass (CPB). However, there is not enough data supporting the superiority of this technique over conventional coronary artery bypass.

Several large non-randomized, retrospective case series comparing OPCAB and conventional coronary artery bypass grafting (CABG) performed with CPB have indicated an advantage of CABG surgery without CPB[5-7]. Similarly a few randomized controlled trials have confirmed that OPCAB is safe but failed to reach a consensus as to the benefits of CABG without CPB[8-10].

However, the selection bias about a lower number of grafts performed in OPCAB patients remains a controversial issue. Several times the off-pump approach was performed in patients with one- or two-vessel disease, whereas CPB was used in patients with multivessel disease. Several retrospective studies comparing OPCAB and on-pump coronary surgery showed a lower number of grafts performed in patients submitted to OPCAB[11-13]. Besides, the largest randomized studies published to date[8-10] show a lower number of grafts performed in OPCAB patients than in on-pump patients. These findings bring about the question of the general applicability of the results.

We eliminated the selection bias correlated with the number of grafts per patient comparing the short-term outcomes of OPCAB and standard CABG patients matched for number of grafts, preoperative risk score according to EuroSCORE, and age.

Methods

Patient selection. Eighty-seven consecutive patients undergoing OPCAB (group A) were selected from the database of our Institution during a 2-year period (May 2000-May 2002). For all patients information necessary for calculation of the EuroSCORE[14] was obtained. Information was also obtained on the number of bypass grafts. Using a patient list from the same database we identified 820 patients who had had a standard CABG operation during the same period. We used this latter database to create a matched cohort of patients. Matching was performed by iterative selection prioritizing, in the following sequence: number of grafts, EuroSCORE, and age. Thus, for a patient who had grafting of three vessels, a sequential group of patients from the 820 patient database was derived. Then, the EuroSCORE was calculated. The database was scrolled until several EuroSCORE matches were found. Then age was used to further select the standard CABG patients with the closest age to the index OPCAB. This process was repeated for each OPCAB patient. A total of 87 patients operated upon with the on-pump technique represented the control group (group B).

During the selection process, the selectors were blinded to patients' outcome. After selection and collection of baseline data, outcome information was obtained.

All cardiac surgery procedures were performed by the same team of surgeons with the assistance of the same team of anesthesiologists and perfusionists. Postoperative care was carried out by the same team of intensivists.

Operative technique. A median sternotomy was performed in all patients. Beating-heart surgery was performed in a standardized fashion as previously described[15]. Briefly, three traction sutures were placed in the posterior pericardium for retraction, followed by placement of a commercially available tissue stabilizer (Medtronic Octopus). The vessel was stabilized, surrounded proximally to the anastomotic site by 5-0 polypropylene sutures to achieve hemostasis after arteriotomy, and it was snared. An intraluminal shunt was used when snaring of the coronary artery was not tolerated. All anastomoses were constructed with a continuous-suture technique with 7-0 or 8-0 monofilament sutures. CABG surgery performed with CPB was done in a standardized fashion with ascending aortic cannulation and two-stage venous cannulation of the right atrium. During CPB, the mean arterial pressure target was set at 60 mmHg, and body temperature was allowed to drift to a minimum of $\approx$ 32°C. Intermittent warm blood cardioplegia was delivered antegradely via the aortic root unless otherwise indicated. In either the CPB or beating-heart approaches, the choice of conduits and construction of composite grafts was based on the surgeon's preference rather than on fixed criteria. Arterial conduits were harvested with minimal trauma (non-skeletonized internal mammary artery), and all were treated with a papaverine solution.

Heparin was given at a dose of 300 IU/kg to achieve a target activated clotting time of > 450 s in the CPB group compared with 200 IU/kg in the beating-heart group. On completion of anastomoses, both groups received protamine sulfate to reverse the effects of heparin and return the activated clotting time to preoperative levels. No special blood conservation techniques were used other than non-hemic prime, retransfusion of all contents of the oxygenator at the end of CPB, and acceptance of normovolemic anemia. Postoperatively, non-hemic volume expanders were used routinely.

Parameters analyzed. The parameters analyzed were: CPB time, coronary occlusion time, number of grafts performed, and the use of the left and right internal mammary arteries. Postoperative data regarding myocardial infarction, reoperation, wound complication, requirements for blood units, intubation time, neurologic dysfunction, requirement of hemofiltration, atrial fibrillation, intensive care unit stay, and in-hospital stay were recorded for both groups. Early mortality was considered as death occurring within 30 days of the procedure.

Statistical analysis. We applied non-parametric statistical analysis to all numerical data and compared groups using the Mann-Whitney U-test. Dichotomous variables in the two groups were compared using the χ^2 test or Fisher's exact test in case of low event frequency. All results are presented as mean ± SD or percentages. A p value of < 0.05 was considered as statistically significant.

Results

The iterative matching process was successful in creating two groups that matched well for all preoperative demographic, clinical, and biochemical features. There were no significant differences in preoperative characteristics between the two groups (Table I).

Intraoperative characteristics. The intraoperative features and outcomes are summarized in table II. The number of grafts per patient was 2.2 ± 0.5 in group A and 2.2 ± 0.5 in group B. The left internal mammary artery anastomosed to the left anterior descending coronary artery was used in 85 (97.7%) patients in group A

Table I. Preoperative characteristics of the study population.

	Group A	Group B	p
No. patients	87	87	
Sex (M/F)	50/37	48/39	0.11
Age (years)	65.9 ± 4.2	64.7 ± 5.2	0.46
Preoperative creatinine (mg/dl)	1.3 ± 0.4	1.4 ± 0.6	0.23
Previous cardiac operation	17 (8.8%)	20 (10.4%)	0.34
Unstable angina	5 (5.7%)	7 (8.0%)	0.42
Ejection fraction < 50%	11 (12.6%)	10 (11.44%)	0.3
Acute myocardial infarction	4 (4.5%)	3 (3.4%)	0.23
Emergency operation	4 (4.5%)	3 (3.4%)	0.42
EuroSCORE	3.4	3.6	0.5

Table II. Intraoperative characteristics of the study population.

Variable	Group A	Group B	p
No. grafts	2.2 ± 0.5	2.2 ± 0.5	NS
Ischemic time (min)	22 ± 11	29 ± 18	0.09

and in 83 (95.4%) patients in group B (p = NS). The right internal mammary artery was used in 40 (45.9%) patients in group A and in 39 (44.8%) patients in group B (p = NS). The saphenous vein was used to complete myocardial revascularization.

The time of extracorporeal circulation was 50 ± 23 min in group B. In group B, the ischemic time was measured by the aortic cross-clamping time and was 29 ± 18 min; in group A it was considered the period of coronary occlusion by coronary snaring and was 22 ± 11 min (p = NS).

Postopeartive morbidity. Diagnosis of myocardial infarction was defined as the occurrence of a new Q wave on the ECG or a creatine kinase-MB elevation above 50 IU/l. The incidence of myocardial infarction did not differ between the two groups. Five (5.7%) patients in group A and 6 (6.8%) patients in group B presented myocardial infarction (p = NS). However, creatine kinase release in groups A and B measured when the patient arrived in the intensive care unit (28 vs 35 IU/l, p = 0.01) and 12 hours postoperatively (37 vs 48 IU/l, p = 0.02) was significantly lower in group A.

Time to extubation did not differ between the two groups (10 ± 4 and 11 ± 4 hours in groups A and B, respectively; p = NS). All alterations causing hypoxia were considered respiratory dysfunction: edema, pneumonia, atelectasis, pneumothorax. Six (6.8%) patients in group A and 7 (8.0%) patients in group B had pulmonary complications (p = NS). No patient in either group had stroke or coma. Ten (11.4%) patients in group A and 17 (19.5%) patients in group B needed blood transfusions (p = 0.001). Five (5.7%) patients in group A and 7 (8.0%) patients in group B had atrial fibrillation (p = NS). There was no difference regarding the incidence of low cardiac output defined as the need of intra-aortic counterpulsation or inotropic drugs for > 24 hours (3 [3.4%] patients in group A and 5 [5.7%] patients in group B, p = NS). Intensive care unit stay was 1.6 ± 1.2 days in patients operated upon with the on-pump technique and 1.4 ± 1.3 days in OPCAB patients (p = NS). Hospital stay was 8.0 ± 1.2 days in group A and 8.1 ± 1.1 days in group B (p = NS). No mediastinitis was observed.

Early mortality did not differ between the two groups (2 [2.2%] patients in group A and 3 [3.4%] patients in group B, p = NS). In group A, 1 patient died of myocardial infarction with cardiogenic shock and another patient died of pneumonia. In group B, 2 patients died of myocardial infarction with cardiogenic shock and another patient died of septic shock.

Discussion

CABG performed with CPB has become a well-established treatment modality for patients with coronary artery disease[16]. However, there has been increasing evidence that CPB may be responsible for some of the morbidity associated with CABG surgery. The systemic inflammatory reaction initiated by the extracorporal circuit results in mechanical trauma to blood, activation of various immunological cascades (complement, cytokines), impaired hemostasis, and impaired neurological, renal, and gastrointestinal function[17,18]. Furthermore, aortic cannulation, cross-clamping, and CPB can result in microembolization and macroembolization with subsequent neurological injury and other end-organ injury, including global myocardial ischemia/reperfusion injury[19]. Thus, it has been proposed that CABG surgery would be safer if CPB was avoided.

However, there is not enough data supporting the superiority of this technique over conventional CABG surgery. Several large, non-randomized, retrospective case series comparing CABG surgery performed on the beating heart (off-pump) and conventional CABG surgery performed with CPB have indicated an advan-

tage of CABG surgery without CPB[1,20-22]. Calafiore et al.[20] reported the results of 1843 consecutive patients undergoing isolated myocardial revascularization. Of the whole study population, 919 patients were operated upon without CPB (group A 49.9%) and 924 patients were operated upon with CPB (group B 50.1%). The early mortality rate was 2.2% (group A 1.4%, group B 3.0%, p = 0.016), the incidence of acute myocardial infarction was 1.8% (group A 1.1%, group B 2.6%, p = 0.027). Using the Society of Thoracic Surgeons National Adult Cardiac Surgery Database, Cleveland et al.[21] reported the results of 126 experienced centers for a total of 118 140 CABG procedures. The number of OPCAB cases was 11 717 (9.9% of total cases). The OPCAB procedure was associated with a decrease in risk-adjusted operative mortality from 2.9% with conventional CABG to 2.3% in the OPCAB group (p < 0.001) and with a decrease in the risk-adjusted major complication rate from 14.15% with conventional CABG to 10.62% in the OPCAB group (p < 0.0001). Using the Department of Veterans Affairs Continuous Improvement in Cardiac Surgery Program records, Plomondon et al.[22] found that OPCAB patients (n = 680) vs on-pump patients (n = 1733) had lower complication rates (8.8 vs 14.0%) and a lower mortality (2.7 vs 4.0%).

However, all these comparative studies reported a number of grafts per patient significantly lower in OPCAB patients. Calafiore et al.[20] reported a number of grafts substantially lower in the OPCAB group (2.4 vs 3.1, p < 0.001). In the series reported by Cleveland et al.[21], 74% of patients operated upon with the on-pump technique had three-vessel disease vs only 47% of OPCAB patients. In the series reported by Plomondon et al.[22], 74% of the patients operated upon with the on-pump technique had three-vessel disease vs only 66% of OPCAB patients.

The largest randomized studies published to date reported conflicting results[8-10]. All of these studies have been modest in size. Furthermore, the only significant differences in outcomes have been almost exclusively in discretionary therapeutic endpoints (blood transfusion, time to extubation, intensive care unit stay, and in-hospital stay), for which bias concerning the assignment to on- or off-pump bypass may have altered thresholds for intervention or discharge. Besides, two randomized studies[8,10] reported a lower number of grafts per patient in OPCAB patients. Légaré et al.[10] reported a mean number of grafts slightly lower for the beating-heart patients than for the on-pump patients (number of grafts/patient 2.8 vs 3.0, p = 0.06). Similar findings were noted by van Dijk et al.[8] (number of grafts/patient 2.4 vs 2.6, p = 0.05). This may reflect the fact that a larger number of patients did not have three-vessel disease in the beating-heart group.

All these findings bring about the question of the general applicability of the results. We eliminated the selection bias correlated with the number of grafts per patient comparing the short-term outcomes of OPCAB and standard CABG patients matched for number of grafts.

We were unable to demonstrate any significant differences in the short-term mortality or morbidity outcome. Our findings have been supported by a meta-analysis[23] of several randomized controlled trials failing to show any significant benefit of CABG performed on the beating heart. Our findings suggest that excellent results can be obtained with both surgical approaches and that the differences noted in previously published studies may have been the result of selection bias due to the number of grafts per patient.

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