Mid-term outcomes of off-pump versus on-pump coronary artery bypass graft surgery

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OBJECTIVE: To evaluate survival and readmissions to hospital for cardiac events or coronary revascularization (REVASC) in patients having off-pump (OPCAB) versus conventional on-pump (CCAB) coronary artery bypass graft surgery (CABG).

METHODS: Of 11,368 consecutive patients undergoing isolated CABG between 1996 and 2002, 514 had OPCAB surgery. Using propensity scores, 503 CCAB patients were randomly matched to 503 OPCAB patients.

RESULTS: There were no clinical or statistical differences between the two groups for any prognostic variable. However, OPCAB patients received significantly fewer distal anastomoses than the CCAB group (2.6 ± 1.0 versus 3.1 ± 1.0 ; $P < 0.001$). There was no difference in operative mortality (OPCAB 1.0%, CCAB 1.4%; $P = 0.6$), but the OPCAB group had significantly fewer operative strokes (0.2% versus 1.8%; $P = 0.01$). Follow-up was 99.7% complete at 2.2 ± 1.2 years (range 0 to 6 years). Twice as many OPCAB patients ($n = 24$) required REVASC compared with the CCAB ($n = 11$) group. The following five-year actuarial outcomes are presented for CCAB and OPCAB, respectively: survival: $77 \pm 6\%$, $76 \pm 8\%$, $P = 0.8$; freedom from REVASC: $95 \pm 3\%$, $92 \pm 2\%$, $P = 0.02$; and cardiac event-free survival: $76 \pm 5\%$, $62 \pm 8\%$; $P = 0.05$. Cox regression revealed that OPCAB was a significant independent predictor of poorer freedom from REVASC (RR 2.2, 95% CI 1.0 to 4.6; $P = 0.04$) and cardiac event-free survival (RR 1.6, 95% CI 1.1 to 2.2; $P = 0.02$).

CONCLUSIONS: The use of OPCAB remains controversial. These results, from this early experience, suggest that despite improved hospital outcomes, the lesser degree of REVASC raises concerns about the need for repeat revascularization in the OPCAB group.

Key Words: Off-pump coronary artery bypass; Survival

Les issues à moyen terme des pontages aortocoronariens à cœur battant par rapport à ceux avec circulation extracorporelle

OBJECTIF : Évaluer la survie et les réhospitalisations en raison d'événements cardiaques ou d'une revascularisation coronaire (REVASC) chez les patients ayant subi un pontage aortocoronarien (PAC) à cœur battant (PACCB) par rapport à un PAC avec circulation extracorporelle (PACCE) classique.

MÉTHODOLOGIE : Des 11 368 patients consécutifs ayant subi un PAC isolé entre 1996 et 2002, 514 avaient subi un PACCB. À l'aide des indices de tendances, 503 patients PACCE ont été appariés de manière aléatoire à 503 patients PACCB.

RÉSULTATS : Les auteurs n'ont observé aucune différence clinique ou statistique entre les deux groupes à l'égard de l'une ou l'autre des variables pronostiques. Cependant, les patients PACCB ont subi beaucoup moins d'anastomoses distales que le groupe PACCE ($2,6 \pm 1,0$ par rapport à $3,1 \pm 1,0$; $P < 0,001$). Il n'y avait pas de différence de mortalité opératoire (PACCB 1,0 %, PACCE 1,4 %; $P = 0,6$), mais le groupe PACCB avait subi beaucoup moins d'accidents cérébrovasculaires opératoires (0,2 % par rapport à 1,8 %; $P = 0,01$). Le suivi était complet à 99,7 % au bout de $2,2 \pm 1,2$ ans (fourchette de 0 à 6 ans). Deux fois plus de patients PACCB ($n = 24$) ont eu besoin d'une REVASC que de patients PACCE ($n = 11$). Les issues actuarielles suivantes au bout de cinq ans sont présentées pour le PACCB et le PACCE, respectivement : survie : 77 ± 6 %, 76 ± 8 %, $P = 0,8$; absence de REVASC : 95 ± 3 %, 92 ± 2 %, $P = 0,02$; et survie sans événements cardiaques : 76 ± 5 %, 62 ± 8 %, $P = 0,05$. La régression de Cox a révélé que le PACCB était un prédicteur indépendant significatif de moindre absence de REVASC (RR 2,2, 95 % IC 1,0 à 4,6, $P = 0,04$) et de survie sans événements cardiaques (RR 1,6, 95 % IC 1,1 à 2,2; $P = 0,02$).

CONCLUSIONS : Le recours au PACCB demeure controversé. Ces résultats, tirés de cette expérience précoce, indiquent que malgré l'amélioration des issues hospitalières, la revascularisation moins marquée soulève des préoccupations quant à la nécessité de reprendre la revascularisation au sein du groupe PACCB.

Coronary artery disease is associated with more death and disabilities than any other disease in industrialized nations. Coronary artery bypass graft surgery (CABG) is one of the most effective methods of treating symptomatic coronary artery disease and is performed in approximately 10,000 patients annually in Ontario.

The majority of cardiac operations require the establishment of cardiopulmonary bypass and cardioplegic arrest. However, cardiopulmonary bypass is a well-recognized factor for generating a whole-body inflammatory response, which can contribute to postoperative morbidity including renal, pulmonary, neurological and bleeding complications (1,2). Benetti et al (3) and Buffolo et al (4) reintroduced beating heart surgery almost 20 years ago as a strategy to prevent complications in high-risk patients. Since that time, off-pump coronary artery bypass (OPCAB) surgery has gained increasing popularity and is challenging

conventional on-pump coronary artery bypass (CCAB) as the standard of therapy for multivessel disease in many cardiac centres (2).

The benefits of OPCAB remain controversial, despite the publication of numerous studies reporting equivalent or improved hospital outcomes and significantly shorter lengths of hospital stay. Ascione and Angelini (5) discussed the dilemma faced by many cardiac surgeons who perform CABG. On one hand, the literature is replete with studies that emphasize the potential for reducing postoperative morbidity and length of stay with OPCAB surgery (6-24); on the other hand, there is continued concern regarding intraoperative myocardial ischemia, inadequate revascularization and the need for early revascularization (5,8,23,25-29).

Therefore, the purpose of the present study was to evaluate mid-term outcomes of OPCAB versus conventional CCAB in two well-matched cohorts.

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METHODS

Patient sample

Between January 1996 and December 2002, 11,368 patients underwent isolated CABG at the University Health Network – Toronto General Hospital (Toronto, Ontario). Of these, 514 patients had surgery performed without cardiopulmonary bypass. All patients had their preoperative, perioperative and hospital clinical outcomes entered prospectively into the cardiac surgery database. The present study was conducted at the Toronto General Hospital and the Institute for Clinical Evaluative Sciences (Toronto), and was approved by the hospital's institutional research ethics board.

Propensity score matching

Calculation of the propensity score: A logistic regression analysis was used to develop a propensity score for OPCAB selection (5,30-37). All prognostic variables (Appendix 1), including a temporal marker and coronary systems grafted, were forced into the logistic regression model so that matching with CCAB patients could be accomplished using all measured variables. Only 52 of 11,368 patients were deleted for missing one or more of the data elements.

The propensity score is defined as the predicted probability that any one patient would be selected for OPCAB surgery. It is calculated from the logistic regression coefficients.

Using only the propensity score, off-pump patients were randomly matched to on-pump patients using a greedy matching strategy (38). Initially, matching was performed based on five decimal places of the propensity score, followed by four-, three-, two- and one-decimal point matching. This yielded 503 OPCAB patients matched to 503 CCAB patients.

Late outcomes

Primary outcome: The primary outcome for the present study was cardiac event-free survival. This was a composite outcome that included any death (including hospital deaths), readmission to hospital for an acute myocardial infarction, readmission to hospital for coronary revascularization (repeat CABG or percutaneous coronary intervention [PCI]) or readmission for stroke.

Administrative data linkage: The Canadian Institute of Health Information contains the discharge *International Classification of Disease* 9th and 10th revision (ICD-9 and ICD-10) codes for every patient admitted to a Canadian hospital. Since 1982, the Division of Cardiovascular Surgery at the Toronto General Hospital has maintained a prospective database for every patient undergoing cardiac surgery at this institution (39-41). The medical record number and the health card number were used to link the clinical database with administrative data to follow all study patients for survival and readmission to hospital for cardiac events. All data linkage and analysis took place at the Institute for Clinical Evaluative Sciences. The closing date for late events was March 31, 2003.

Deaths were determined from three sources:

- operative mortality, defined as any in-hospital death in the clinical registry during the index admission for CABG;
- in-hospital deaths from the Canadian Institute of Health Information database were determined from the discharge exit code; and
- out-of-hospital deaths were determined from the Registered Persons Data Base.

Readmissions to hospital for cardiac events occurring after the entry date of operation were determined from the ICD-9 and ICD-10 codes for the most responsible diagnosis and the revised Canadian Classification of Diagnostic procedure codes for the revascularization procedures (42,43).

The first admission for each cardiac event was captured and used in the analysis; therefore, any patient could have had more than one type

of cardiac event analyzed. The failure time for freedom from any cardiac event was defined as the earliest readmission date for any cardiac event.

Statistical analysis

SAS 8.2 for Windows (SAS Institute, USA) was used for all data analysis. Results are reported as the mean $\pm$ 1 SD in the tables and text, and as the mean $\pm$ 1 SEM in the figures. Continuous variables were analyzed by unpaired *t* tests. Categorical variables are reported as proportions and were analyzed using χ^2 or Fisher's exact test, where appropriate. Time-to-event outcomes were analyzed univariately by the Kaplan-Meier method and multivariately by Cox regression. The *P* value for significance was 0.05. The present study had 80% power to detect a 20% risk reduction in time-to-event outcomes.

RESULTS

Effectiveness of matching

A comparison of the 503 matched pairs is contained in Table 1. Patients were very similar and, unlike previous studies (19), they were matched for major coronary vessels grafted, peripheral vascular disease, previous stroke or transient ischemic attack, and year of operation. However, despite a similar extent of coronary artery disease, OPCAB patients received significantly fewer bypass grafts than CCAB patients.

Hospital outcomes

OPCAB patients had significantly shorter intensive care unit and total length of hospital stays (Table 2). Hospital mortality was similar between the two groups. However, OPCAB patients had significantly fewer strokes. Reoperation for bleeding was higher in the OPCAB group. The reason for more bleeding in the OPCAB group is unclear from the analysis, but it may be related to a pattern of practice by anesthesiology to avoid giving antifibrinolytics to this group at the time of surgery.

Late outcomes

Three out-of-province patients were lost to follow-up. The length of follow-up was similar in both groups: CCAB 2.2 ± 1.2 years, OPCAB 2.2 ± 1.3 years ($P=0.4$). The range of follow-up was zero to six years. Seventy patients died (35 in each group). The five-year survival (Figure 1) was $77 \pm 6\%$ in the CCAB group and $76 \pm 8\%$ in the OPCAB group ($P=0.8$).

Twice as many OPCAB patients required coronary revascularization ($n=24$; CABG $n=12$, PCI $n=16$) compared with the CCAB group ($n=11$; CABG $n=4$, PCI $n=8$). Some patients required both PCI and repeat CABG. The five-year freedom from repeat coronary revascularization (Figure 2) was $95 \pm 3\%$ in the CCAB group and $92 \pm 2\%$ in the OPCAB group ($P=0.025$). OPCAB was a significant independent predictor of the need for repeat revascularization (RR 2.2; 95% CI 1.0 to 4.6; $P=0.038$).

There was a similar number of readmissions for acute myocardial infarction (CCAB $n=14$, OPCAB $n=12$). Freedom from acute myocardial infarction at five years was $90 \pm 5\%$ in the CCAB group and $87 \pm 7\%$ in the OPCAB group ($P=0.8$). There was no significant difference between the two groups for stroke readmissions: five-year estimates were $98 \pm 1\%$ in the CCAB group and $94 \pm 2\%$ in the OPCAB group ($P=0.2$).

There was a significant difference in cardiac event-free survival between the two groups (CCAB $n=50$, OPCAB $n=65$) (Figure 3). Five-year cardiac event-free survival was $76 \pm 5\%$ in the CCAB group and $62 \pm 8\%$ in the OPCAB group ($P=0.05$). OPCAB was a significant independent predictor of death or readmission for a cardiac event (RR 1.55; 95% CI 1.1 to 2.2; $P=0.05$).

DISCUSSION

The level of existing evidence regarding the benefits of off-pump CABG is controversial. There are several small randomized trials (6-12) that reported less operative morbidity, shorter lengths of hospital stay

TABLE 1
Propensity score, pair-wise-matched sample of patients undergoing isolated off-pump (OPCAB) and on-pump (CCAB) coronary artery bypass graft surgery between 1996 and 2002 at the University Health Network – Toronto General Hospital

Variable	CCAB (n=503)	OPCAB (n=503)	P
Age, years*	63±10	63±10	0.6
Body surface area, m ² *	1.92±0.2	1.91±0.2	0.3
Body mass index, kg/m ² *	28±7	28±5	0.8
CBP time, min*	83±29	0	<0.001
Cross-clamp time, min*	60±22	0	<0.001
Female sex, %	23	26	0.4
Left ventricular grade			
1	45	45	
2	35	34	
3	18	19	
4	2	2	0.9
Surgical priority			
Elective	52	55	
Urgent	47	45	
Emergent	0.2	0.2	0.8
Recent myocardial infarction†	17	18	0.6
New York Heart Association classification			
I	9	9	
II	16	18	
III	18	18	
IV	58	56	0.8
Number of diseased vessels			
1	14	16	
2	29	28	
3	57	56	0.7
Left main disease	20	20	1.0
Redo coronary artery bypass graft surgery	3.6	3.6	1.0
Renal insufficiency	6.6	6.2	0.8
Congestive heart failure	6.6	7.0	0.8
Diabetes	30	30	1.0
Peripheral vascular disease	34	36	0.6
Hypertension	58	56	0.4
Chronic obstructive lung disease	4	4	1.0
Preoperative stroke/TIA	9.2	10	0.7
Year of operation			
1996–1998	9	13	
1999–2000	65	62	
2001–2002	26	26	0.1
Number of distal anastomoses			
1	5.2	10	
2	23	13	
3	36	33	
4	29	18	
5	6	3	<0.001
Number of grafts*	3.1±1.0	2.6±1.0	<0.001
Coronary system grafted			
Left anterior descending artery	97	96	0.7
Circumflex coronary artery	62	61	0.7
Right coronary artery	38	39	0.7
Left internal thoracic artery	89	88	0.8
RITA	5.2	8.0	0.07
LITA + RITA	4.6	7.4	0.06

*Reported as mean ± SD; †Within one month before surgery. CBP Cardiopulmonary bypass; LITA Left internal thoracic artery; RITA Right internal thoracic artery; TIA Transient cerebral ischemic attack

TABLE 2
Hospital outcomes

	CCAB	OPCAB	P
Ventilation time, h*	14±30	10±23	0.036
Intensive care unit stay, days*	2.0±3.4	1.7±2.2	0.052
Total length of stay, days*	7.7±6.2	6.8±5.5	0.017
Hospital mortality, %	1.4	1.0	0.6
Myocardial infarction, %	2.2	3.6	0.2
Low cardiac output syndrome, %	4.8	3.4	0.3
Stroke, %	1.8	0.2	0.011
Postoperative renal failure, %	0.8	0.8	0.6
Reopened for bleeding, %	1.8	4.6	0.012

*Reported as mean ± SD. CCAB On-pump coronary artery bypass; OPCAB Off-pump coronary artery bypass

Figure 1) Survival estimates for conventional coronary artery bypass (CCAB) depicted by the solid line and off-pump coronary artery bypass (OPCAB) depicted by the dashed line. Patients at risk at one, three and five years (yr), respectively, for CCAB: 397, 118 and 17; and OPCAB: 404, 116 and 12

Figure 2) Freedom from coronary revascularization (REVASC) (defined as repeat coronary artery bypass or percutaneous coronary intervention). CCAB Conventional coronary artery bypass; OPCAB Off-pump coronary artery bypass; yr Years

Figure 3 Cardiac event-free survival (defined as freedom from death or readmission to hospital for acute myocardial infarction, repeat coronary intervention or stroke). CCAB Conventional coronary artery bypass; OPCAB Off-pump coronary artery bypass; yr Years

and reduced costs with OPCAB. In a meta-analysis of nine randomized controlled trials, Parolari et al (2) evaluated a composite hospital end point (death, stroke or myocardial infarction) in 532 patients randomly assigned to OPCAB and 558 patients randomly assigned to CCAB. They found a trend toward a risk reduction associated with OPCAB for the composite outcome (OR 0.48; 95% CI 0.21 to 1.09; $P=0.08$). However, a more recent randomized controlled trial by Legare et al (44) failed to demonstrate any short-term advantage to OPCAB.

In contrast, Czerny et al (25) found that 35% of patients (14 of 40) randomly assigned to the OPCAB arm had to be switched to CCAB because of deep myocardial vessels or hemodynamic instability. In addition, 11.5% of the remaining OPCAB patients (three of 26) required percutaneous transluminal angioplasty within three months of surgery versus none in the CCAB group. They concluded that the rate of incomplete revascularization was high and compromised the basic principle of complete revascularization in patients requiring CABG. Although hospital outcomes reported from randomized trials for OPCAB are mostly favourable, the length of follow-up tends to be too short and the sample sizes insufficiently powered to detect differences in late outcomes.

Observational studies generally have much larger sample sizes, and when proper multivariable statistical methods are employed, demonstrate a similar risk reduction for in-hospital outcomes for OPCAB surgery (13-20). However, such studies are frequently limited by the fact that patients who 'cross over' to CCAB, usually due to hemodynamic instability or other intraoperative difficulties, are frequently not identified a priori. Such patients represent a very high-risk cohort and invariably result in worse outcomes for the on-pump group. Most larger contemporary observational studies do not report late clinical outcomes. Hence, the dilemma faced by many cardiac surgeons: without clear evidence of late outcomes, it is difficult to weigh the risks and benefits of OPCAB surgery.

The results of the present study were similar to those found in an early small observational study of consecutive patients operated on between 1989 and 1990 by Gundry et al (26). They found that survival was equivalent at seven years, but OPCAB patients were almost three times more likely to require revascularization (20%) compared with CCAB patients (7%; $P=0.01$). In fact, six of 101 OPCAB patients (5.6%) required repeat CABG compared with none in the CCAB group ($P=0.01$). There was, on average, one fewer graft per OPCAB patient compared with the CCAB group. A larger observational study by Williams et al (27) also demonstrated

an increased risk for repeat revascularization with OPCAB surgery (RR 1.29, $P=0.02$). Other studies (23,27,28) have reported similar increased need for early revascularization following OPCAB. The increased need for repeat revascularization may outweigh any potential economic benefits of earlier intensive care unit and hospital discharge. This concern may have factored into the results found by Desai et al (29), who conducted a population-based survey of Canadian cardiac surgeons and found that on-pump bypass was still the preferred strategy.

Ascione and Angelini (5) offer a cautionary note in their editorial. They stated that OPCAB is being performed in thousands of patients every year, resulting in a possible reduction in-hospital morbidity and in-hospital costs of up to 25%. However, the evidence regarding long-term outcomes is still inconclusive. They suggested that if the evidence is against OPCAB, those surgeons performing this procedure should stop because they are affecting the quality of care of thousands of patients worldwide. If, on the other hand, the evidence from long-term studies supports OPCAB, training programs should support the implementation of OPCAB.

The issue of a lack of long-term clinical outcomes in OPCAB surgery cannot be overstated. The present study was designed to provide timely information, for a well-matched OPCAB and CCAB patient sample, regarding survival and readmission to hospital for cardiac events, not the least of which is the need for repeat revascularization.

Limitations

The limitations of the present study include those associated with observational studies, in that we can only adjust for those variables measured. In addition, OPCAB was not uniformly applied to a specific patient population; therefore, some selection bias may be present that was not factored into the propensity score-matching procedure. One surgeon at our institution routinely performed off-pump surgery during the study period and accounted for 75% of the total OPCAB patient population. Other surgeons generally performed off-pump surgery only in those patients who were considered to be high-risk for on-pump revascularization (eg, patients with ascending aorta atherosclerosis). It is important to note, however, that patients who required ascending aorta repair were not included in the present study, and that we did not find any surgeon-related effects in our analysis of outcomes.

One potential criticism of our methods may be that we included patients from the 'learning curve'. While eliminating patients from the learning curve is an acceptable method for randomized controlled trials, it is not, in our opinion, acceptable for observational studies. By definition, observational studies evaluate 'real-world' experience: eliminating early patients and their outcomes may potentially introduce another level of bias. Outcomes of CABG have improved nationwide over the past decade; these patients were matched on year of operation, and hopefully this manoeuvre helped to mitigate some of the potential learning curve issues.

CONCLUSION

OPCAB surgery was associated with shorter hospital lengths of stay and fewer operative strokes. However, the issue of incomplete revascularization remains a concern, because OPCAB was associated with a higher rate of repeat revascularization and poorer cardiac event-free survival in these early patients.

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APPENDIX 1

Variables forced into the logistic regression model for off-pump coronary artery bypass (OPCAB) selection

Age at operation (years)
 Sex: male/female
 Left ventricular grade
 1 – Left ventricular ejection fraction >60%,
 2 – Left ventricular ejection fraction 40% to 59%
 3 – Left ventricular ejection fraction 20% to 39%
 4 – Left ventricular ejection fraction <20%
 Surgical priority
 Elective
 Urgent (same hospitalization as cardiac catheterization or cardiac event)
 Emergent (within 12 h of cardiac catheterization or a cardiac event)
 New York Heart Association classification for symptoms (I to IV)
 Recent myocardial infarction (within one month before surgery)
 Previous coronary artery bypass graft surgery
 Number of major coronary artery systems diseased (one, two or three)
 Left main coronary artery disease (>50% stenosis)
 Presence of congestive heart failure
 Renal insufficiency: renal dialysis or serum creatinine >150 µmol/L
 Diabetes controlled by medication
 Peripheral vascular disease, including disease of the carotid artery
 Chronic obstructive pulmonary disease
 History of hypertension
 History of a cerebral stroke or transient ischemic attack
 Vessels grafted: any distal anastomosis to major coronary system
 (left anterior descending, right coronary artery, circumflex)
 Year of operation (1996 to 1998, 1999 to 2000, 2001 to 2002)

These variables were forced into a logistic regression analysis to calculate the predicted probability that any patient would be selected for OPCAB surgery. The predicted probability for OPCAB selection = the propensity score. A group of patients with the same propensity score for OPCAB selection are therefore equally likely to have been assigned to the conventional coronary artery bypass (CCAB; control) group. Each OPCAB patient was randomly matched to a CCAB patient by the propensity score

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