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Long-term Survival and Cardiac Troponin T Elevation in On- and Off-Pump Coronary Artery Bypass Surgery

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ABSTRACT

Introduction. The long-term clinical usefulness of conventional coronary artery bypass graft surgery (CCAB) versus off-pump surgery (OPCAB) remains controversial. Long-term survival and elevation in cardiac troponin T (cTnT) concentration following CCAB and OPCAB have not been assessed. We tested the hypothesis that long-term survival rates for CCAB and OPCAB patients were similar when stratified by cTnT concentration.

Methods and Results. In this prospective cohort, we followed 1511 nonemergency patients with 2- or 3-vessel disease (778 CCAB and 733 OPCAB cases) from a hospital in northern New England to determine if 6-year survival rates for CCAB and OPCAB patients were similar. The patients underwent surgery between 2000 and 2004 by surgeons who used both procedures. Postoperative cTnT elevation was defined as ≥1 ng/mL, the upper quartile of cTnT values. Data were linked to the Social Security Administration Death Master File. Kaplan-Meier analysis and Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI), with adjustments for baseline patient and disease characteristics. Patients were followed for a median of 4.1 years (mean, 4.0 years). Patients were similar with regard to baseline disease characteristics, comorbidities, cardiac history, function, and anatomy. OPCAB was associated with increased rates of postoperative bleeding and with a worse 6-year survival rate compared with CCAB, regardless of cTnT concentration (cTnT <1 ng/mL, $P < .013$; cTnT ≥1 ng/mL, $P = .017$). Compared with CCAB patients, the adjusted HR (95% CI) was 1.59 (1.09-2.32) for OPCAB patients with cTnT concentrations <1 ng/mL and 1.93 (1.12-3.31) for OPCAB patients with cTnT concentrations ≥1 ng/mL.

Conclusion. Survival is better for CCAB patients than for OPCAB patients, regardless of cTnT concentration. This effect is sustained after multivariable adjustment for baseline mortality risk factors.

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INTRODUCTION

Coronary artery bypass graft surgery (CABG) is commonly carried out with cardiopulmonary bypass. Over the past 10 years, off-pump CABG (OPCAB) has decreased in popularity as an alternative to conventional CABG (CCAB). OPCAB was developed with the hope of reducing the occurrence of myocardial injury, inflammation [Matata 2000; Biglioli 2003; Okubo 2003], stroke [Mazzone 2003], and renal failure [Tang 2002]. Two recent meta-analyses have demonstrated no clinical benefit of OPCAB over CCAB with respect to short- and long-term survival and morbidity [van der Heijden 2004; Wijeysundera 2005].

Although there continues to be a lack of clinical evidence favoring OPCAB for any group of patients, the OPCAB approach has been shown to reduce myocardial injury, as evidenced by the release of cardiac troponin T (cTnT) following surgery [Bennetts 2002; Brown 2007]. cTnT is a highly sensitive and specific marker of myocardial injury [Kathiresan 2004]. These findings have suggested that OPCAB produces less myocardial injury and therefore may have a survival benefit compared with CCAB; however, no study has adequately documented long-term survival for patients who have undergone these procedures with respect to changes in cTnT concentration following surgery. Therefore, we sought to discern whether survival was significantly better in OPCAB patients, with or without an elevation in cTnT concentration.

MATERIALS AND METHODS

Data Collection

The Northern New England Cardiovascular Disease Study Group (NNECDSG) was founded in 1987 as a regional voluntary consortium to evaluate 100% of the coronary revascularizations and/or valve procedures

performed in northern New England, including 8 medical centers in Vermont, New Hampshire, and Maine. The group consists of clinicians, hospital administrators, and health care research personnel who seek continuing improvement in the quality, safety, effectiveness, and costs of medical interventions for treating cardiovascular disease. The Institutional Review Board approved the NNECDSG for data collection and analysis.

Between January 2000 and June 2004, we prospectively enrolled 1511 consecutive CCAB and OPCAB procedures at a single medical center. There were 778 CCAB and 733 OPCAB procedures during the study period. cTnT concentrations were measured 24 hours after the surgery.

Data were collected as previously described [Hernandez 2000, 2001] and recorded prospectively for all patients. Cardiac catheterizations were carried out during the course of regular clinical care and used standard methods. The number of diseased coronary vessels was assessed according to criteria established by the National Heart, Lung, and Blood Institute Coronary Artery Surgery Study [Killip 1981]. The priority for surgical procedure was assessed by the cardiothoracic surgeons as previously described [O'Connor 1991; Surgenor 2001].

For this research, we excluded patients who underwent myocardial revascularization in association with heart valve repair, resection of ventricular aneurysm, or another surgical procedure (n = 686). We excluded patients who had undergone their operations with surgeons who had performed fewer than 100 OPCAB procedures during the study period (n = 407). This criterion restricted our analyses to CCAB and OPCAB operations by surgeons who perform high volumes of both kinds of procedures. We excluded emergent patients (n = 90).

Surgical Procedures

The surgical methods have previously been described [Hernandez 2000, 2001]. The decision to perform the operation with or without a heart-lung machine was made by the operating surgeon. All procedures were done via a median sternotomy incision. The choices of conduit used and vessels grafted were made by the surgeon. Heparin doses varied with the surgeon. Various techniques were used to afford exposure to the coronary artery segments, and the choice of the several available retractor-stabilizer systems was made according to each surgeon's preference. The management of CCAB cases was standardized with regard to cardiopulmonary bypass parameters, use of hypothermia, and the myocardial protection technique used.

The Medtronic Octopus (Medtronic, Minneapolis, MN, USA) and the Genzyme Cohn Cardiac Stabilizer (Genzyme, Cambridge, MA, USA) systems were used for OPCAB procedures. Shunts were rarely used. Only small sections of the myocardium (the area just distal to the artery being bypassed at the point of the anastomosis) were made ischemic, and then only briefly (the time required to perform that particular distal anastomosis). Once the anastomosis was completed, the affected area of myocardium was reperfused while the remainder of the operation was performed.

Cardiac Troponin T

Postoperative cTnT concentrations were measured in the intensive care unit 24 hours later, on the morning after the surgery. The clinical laboratory measured cTnT levels immediately after sample collection with reagents from Roche Diagnostics (Indianapolis, IN, USA). We report cTnT data as the geometric mean (nanograms per milliliter). The lower limit of this assay was 0.01 ng/mL, and the threshold for diagnosing myocardial necrosis was 0.20 ng/mL [Coudrey 1998; Bennetts 2002].

Survival and Statistical Analysis

The goal of this research was to compare OPCAB and CCAB survival rates according to the elevation in cTnT concentration. The threshold for an elevated cTnT concentration was defined as the upper quartile value (1.0 ng/mL). χ^2 tests and unpaired Student *t* tests were used to examine differences between CCAB and OPCAB operations with respect to patient and disease characteristics. Survival data were obtained via a link to the Social Security Association Death Master File (SSADMF), which had survival information complete through August 31, 2006. Kaplan-Meier and log-rank methods of survival analysis were used to test differences in 6-year survival rates. We used Cox proportional hazards modeling to test the difference between OPCAB and CCAB across the survival function, with and without adjustment for baseline risk factors for survival. Cox proportional hazards modeling was used to independently test the effect of cTnT on 6-year survival, irrespective of OPCAB or CCAB operation and patient and disease characteristics. The data were analyzed with Stata software (release 9.0; Stata, College Station, TX, USA).

RESULTS

We prospectively followed 778 CCAB patients and 733 OPCAB patients for a mean of 4.0 years (median, 4.1 years). Of these operations, 675 OPCAB and 330 CCAB patients experienced no elevation in cTnT concentration (cTnT <1.0 ng/mL), and 58 OPCAB and 448 CCAB patients showed an elevated cTnT concentration (cTnT ≥1.0 ng/mL). The patients in the 2 surgery groups were similar with regard to age, sex, and body mass index (Table 1). The 2 groups of patients had similar comorbidities, which included vascular disease, diabetes, renal function, chronic obstructive pulmonary disease, and urgent priority (Table 2). The 2 groups were also similar with regard to ejection fraction, prior CABG surgery, left main coronary artery disease, and left anterior descending coronary artery disease. The OPCAB and CCAB groups differed with respect to the number of diseased vessels and the numbers of diseased vessels including the right coronary, circumflex, and posterior descending arteries (Table 3). Procedural data showed that the OPCAB and CCAB groups did not differ with respect to the ratio of the number of distal anastomoses to the number of diseased vessels or in the proportion of operations that used the internal mammary artery (Table 4). The OPCAB and CCAB groups also were not different with respect to the preoperative predicted mortality risk, as assessed with the NNECDSG preoperative

Table 1. Patient Characteristics*

	CCAB (n = 778), %	OPCAB (n = 733), %	P†
Patient age			
<60 y	31.0	28.8	.469
60-69 y	32.0	32.2	
70-79 y	31.1	31.2	
≥80 y	5.9	7.8	
Female patients	25.1	28.1	.181
Body mass index			
<31	67.2	69.2	.755
31-36	24.3	22.9	
≥37	8.0	7.6	

*CCAB indicates conventional coronary artery bypass graft surgery; OPCAB, off-pump coronary artery bypass graft surgery.

†*P* for χ^2 test.

mortality model [O'Connor 1992]. The data summarized in Tables 1 to 4 demonstrate that the OPCAB and CCAB patients were similar with regard to baseline disease characteristics; however, significantly more patients with 3-vessel disease underwent CCAB.

An elevated cTnT concentration (cTnT >1.0 ng/mL) was seen more frequently in the CCAB group (OPCAB, 58 patients; CCAB, 448 patients). Patients with an elevated cTnT concentration had a lower survival rate (*P* = .09, Figure 1). cTnT concentration was an independent (procedure type, age, and sex) predictor of long-term survival, with an adjusted hazard ratio (HR) of 1.29 (95% confidence interval [CI], 1.17-2.06) for each 1.0-ng/mL increase in cTnT concentration (Table 5).

The CCAB group had significantly better adjusted overall survival than the OPCAB group (*P* = .037; Figure 2) and had significantly better adjusted 6-year survival among the patients without an elevation in cTnT concentration (*P* = .013, Figure 3A). The 1-, 3-, and 6-year survival rates for the patients in the OPCAB group without an elevation in cTnT concentration were 94%, 88%, and 74%, respectively, whereas the corresponding survival rates for the CCAB group were 96%, 92%, and 87%. Among the patients with an elevated cTnT concentration, the 6-year survival rate was significantly better for the CCAB patients than for the OPCAB patients (*P* = .017, Figure 3B). The 1-, 3-, and 6-year survival rates for the patients in the OPCAB group with an elevated cTnT concentration were 86%, 79%, and 65%, respectively, and the corresponding rates in the CCAB group were 94%, 88%, and 83%. After HR adjustment for baseline risk factors (Table 5), the overall adjusted HR for the OPCAB group was 1.37 (95% CI, 1.05-1.79). The adjusted HR were 1.59 (95% CI, 1.09-2.32) for the OPCAB patients without an elevated cTnT concentration and 1.93 (95% CI, 1.12-3.31) for the OPCAB patients with an elevated cTnT concentration.

Table 2. Patient Comorbidities*

	CCAB, %	OPCAB, %	P†
Vascular disease	23.4	26.1	.230
Diabetes	34.8	34.0	.724
Preoperative renal failure or creatinine ≥2 mg/dL	3.1	2.7	.681
COPD	6.4	8.3	.158
Urgent operation	67.1	64.1	.224

*CCAB indicates conventional coronary artery bypass graft surgery; OPCAB, off-pump coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease.

†*P* for χ^2 test.

Table 3. Cardiac History, Function, and Anatomy*

	CCAB, %	OPCAB, %	P†
Ejection fraction <0.40	9.4	7.9	.314
Prior CABG	2.1	1.4	.301
No. of diseased vessels			
2	28.8	30.8	.386
3	59.1	52.8	.013
Coronary artery stenosis			
Left main ≥50%	27.1	25.8	.556
LAD ≥70%	85.4	86.1	.682
RCA ≥70%	82.4	78.0	.033
CX ≥70%	73.5	67.4	.009
PDA ≥70%	5.1	1.4	<.001

*CCAB indicates conventional coronary artery bypass graft surgery; OPCAB, off-pump coronary artery bypass graft surgery; CABG, coronary artery bypass grafting; LAD, left anterior descending coronary artery; RCA, right coronary artery; CX, left circumflex coronary artery; PDA, posterior descending coronary artery.

†*P* for χ^2 test, Student *t* test.

DISCUSSION

We sought to demonstrate a survival benefit for OPCAB procedures, compared with CCAB, for patients who had less myocardial injury as evidenced by cTnT release. We found,

Table 4. Procedural Data and Predicted Risk*

	CCAB	OPCAB	P†
No. of distal anastomoses	3.3	3.0	<.001
No. of distal anastomoses per no. of diseased vessels	1.4	1.4	.181
IMA used, %	94.6	92.6	.117
Mean predicted mortality risk	2.4	2.4	.977

*The predicted-risk model includes age, sex, body mass index, peripheral vascular disease, diabetes, preexisting renal failure or creatinine ≥2 mg/dL, chronic obstructive pulmonary disease, prior coronary artery bypass grafting surgery, preoperative ejection fraction <0.40, left main stenosis ≥50%, and number of diseased vessels. CCAB indicates conventional coronary artery bypass graft surgery; OPCAB, off-pump coronary artery bypass graft surgery; IMA, internal mammary artery.

†*P* for χ^2 test, Student *t* test.

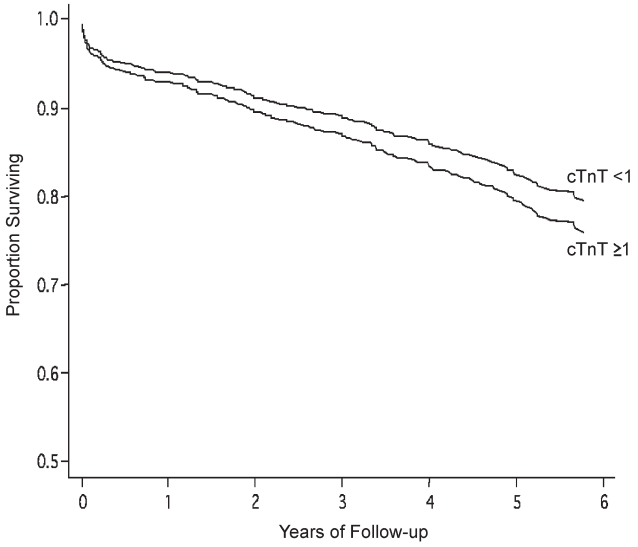

Figure 1. Kaplan-Meier survival plot for all patients, both for those who underwent off-pump coronary artery bypass grafting surgery and for patients who underwent conventional coronary artery bypass graft surgery. The Kaplan-Meier survival plot is stratified by cardiac troponin T (cTnT) concentration (<1 ng/mL, ≥1 ng/mL) and is adjusted for age and sex.

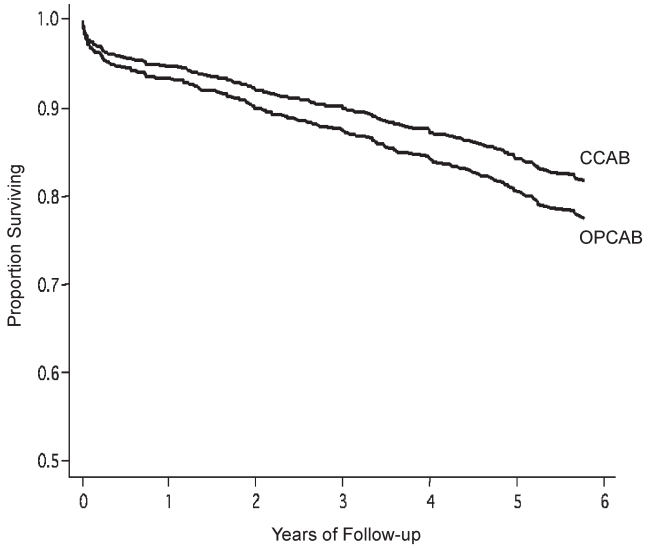

Figure 2. Kaplan-Meier survival plot for all patients. Plot is stratified by patients who underwent off-pump coronary artery bypass grafting surgery (OPCAB) and those who underwent conventional coronary artery bypass graft surgery (CCAB) and is adjusted for age and sex.

however, that patients in the CCAB group had significantly better 6-year survival than those in the OPCAB group, for both patients with and those without an elevated cTnT concentration following isolated CABG. We also found cTnT concentration to be a continuous independent predictor of 6-year survival, with a 29% increased risk of death for each 1.0 ng/mL increase in cTnT concentration.

Table 5. Survival Analysis*

	Adjusted HR	95% CI	*P*
All patients			
cTnT <1 ng/mL	1.00	—	
cTnT ≥1 ng/mL	1.20	0.91-1.58	.205
All patients			
CCAB	1.00	—	
OPCAB	1.29	0.99-1.68	.064
Patients with cTnT <1 ng/mL			
CCAB	1.00	—	
OPCAB	1.48	1.02-2.16	.041
Patients with cTnT ≥1 ng/mL			
CCAB	1.00	—	
OPCAB	1.87	1.08-3.23	.024
Full model			
OPCAB (versus CCAB)	1.55	1.17-2.06	.002
cTnT (1.0-ng/mL decrease)	1.29	1.16-1.42	<.001
Age	1.07	1.05-1.08	<.001
Sex	1.00	0.76-1.33	.982

*Hazard ratios (HR) are adjusted for age and sex. CI indicates confidence interval; cTnT, cardiac troponin T; CCAB indicates conventional coronary artery bypass graft surgery; OPCAB, off-pump coronary artery bypass graft surgery.

The OPCAB procedure has been associated with significantly less enzyme release than on-pump surgery [Bennetts 2002; Brown 2007], and there are several reasons to expect myocardial enzyme release during bypass surgeries. For CCAB, the magnitude of the cTnT release measured at 24 hours postoperatively is directly associated with the ischemic time. In our cohort, we found the cTnT concentration to be correlated with cross-clamp time ($r = 0.13$; $P < .001$). In OPCAB cases, enzyme release can be due to incomplete revascularization or graft failure [Paparella 2007]. We demonstrated that the OPCAB patients had fewer distal anastomoses than the CCAB patients (Table 3). Khan et al [2004] showed that CCAB patients had significantly better graft patency at 3 months than OPCAB patients (98% versus 88%). A similar effect in our cohort would explain the consistent survival advantage experienced by CCAB patients. OPCAB was also associated with an increased risk of bleeding complications, both with (7%, OPCAB; 2%, CCAB) and without (6%, OPCAB; 3%, CCAB) an elevated cTnT concentration. Bleeding complications were not an independent predictor of 6-year survival in the Cox proportional hazards model, however. During the index admission period, the OPCAB and CCAB groups were not significantly different with respect to the incidence of low-output failure; however, low-output failure was a statistically significant predictor of 6-year survival in the patients with elevated cTnT concentrations (HR, 6.99; 95% CI, 4.12-11.85).

Our results differ from those of previous studies that demonstrated a survival advantage for on-pump surgery. Hannan et al [2007] recently reported that CCAB patients had significantly better 3-year survival than OPCAB patients;

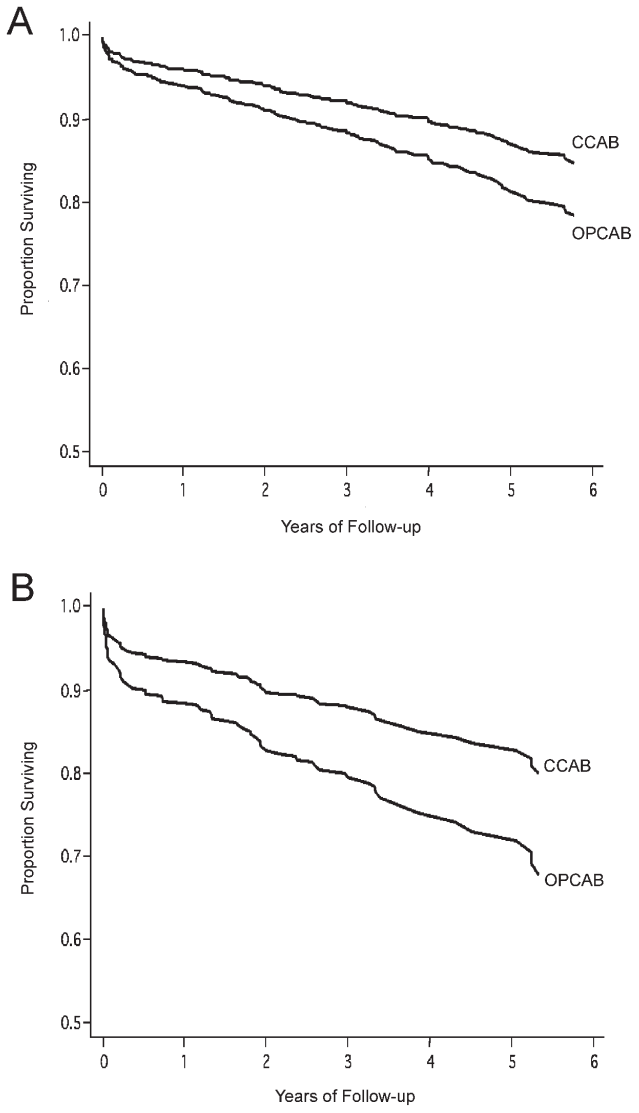

Figure 3. Kaplan-Meier survival plots for off-pump coronary artery bypass grafting surgery (OPCAB) patients and those who underwent conventional coronary artery bypass graft surgery (CCAB), according to the elevation in cardiac troponin T (cTnT) concentration. A, Survival plot for patients with no elevation in the cTnT concentration (ie, <1.0 ng/mL) measured 24 hours after surgery (adjusted for age and sex). B, Survival plot for patients with an elevation in cTnT concentration (≥1.0 ng/mL) measured at 24 hours after surgery (adjusted for age and sex).

however, this effect was removed after adjustment. Our findings show that CCAB shows improved 6-year survival even after adjustment for baseline risk factors, and this result is independent of the cTnT concentration measured at 24 hours after surgery. Lahtinen et al [2007] noted that propensity score–matched OPCAB patients had a greater elevation in cardiac troponin I concentration than CCAB patients (117 versus 58 ng/mL) and a worse 2-year survival rate (84.9% versus 89.2%). Two meta-analyses have shown no statistically significant survival advantage for OPCAB over CCAB for the randomized controlled trials (relative risk, 0.82; 95% CI, 0.40-1.68) [van der Heijden 2004; Wijeysundera 2005]. Our cohort accurately reflects the general patient population that presents for surgery. This study is the first to report 6-year survival data for OPCAB and CCAB patients, with and without elevated cTnT concentrations following surgery. We believe that these findings show a survival advantage for CCAB patients compared with patients who undergo OPCAB and demonstrate the predictive importance of a postoperative assessment of myocardial enzymes 24 hours after surgery.

There are limitations to our findings. We lack angiographic follow-up patient data to evaluate the graft patencies in the 2 groups. The natural comparison in our cohort is not a true randomization of patients, but rather a representation of the underlying population of patients who undergo OPCAB and CCAB procedures and have similar characteristics, diseases, and comorbidities.

In conclusion, on-pump surgery was associated with statistically significantly better survival than off-pump surgery for a representative cohort of patients who underwent on- or off-pump CABG surgery, and this finding was independent of any elevation in the cTnT concentration measured 24 hours after surgery. OPCAB should be reserved for patients who would benefit from not using an aorta cross-clamp or cardiopulmonary bypass, such as elderly or female patients at risk of stroke or those who have known atherosclerosis of the aorta [Lytle 2007]. Cardiac troponin concentrations should be measured within 24 hours after the surgical procedure to monitor the risk for mortality.

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