Does off-pump coronary surgery reduce morbidity and mortality?

Joseph F. Sabik, MD
A. Marc Gillinov, MD
Eugene H. Blackstone, MD
Catherine Vacha, RN, BSN
Penny L. Houghtaling, MS
Jose Navia, MD
Nicholas G. Smedira, MD
Patrick M. McCarthy, MD
Delos M. Cosgrove, MD
Bruce W. Lytle, MD

See related editorial on page 655.

From the Departments of Thoracic and Cardiovascular Surgery and Biostatistics and Epidemiology, The Cleveland Clinic Foundation, Cleveland, Ohio.

Partial funding of nursing personnel for data collection of the off-pump cases was provided by Guidant Corporation, which otherwise had no input into the analyses and did not review or endorse the results reported in this study.

Read at the Eighty-first Annual Meeting of The American Association for Thoracic Surgery, San Diego, Calif, May 6-9, 2001.

Received for publication May 15, 2001; revisions requested July 31, 2001; revisions received Oct 12, 2001; accepted for publication Oct 24, 2001.

Address for reprints: Joseph F. Sabik, MD, The Department of Thoracic and Cardiovascular Surgery, The Cleveland Clinic Foundation, 9500 Euclid Ave, Desk F25, Cleveland, OH 44195 (E-mail: sabikj@ccf.org).

J Thorac Cardiovasc Surg 2002;124:698-707

Copyright © 2002 by The American Association for Thoracic Surgery

0022-5223/2002 \$35.00+0 12/6/121975

doi:10.1067/mtc.2002.121975

Objective: To compare hospital outcomes of on-pump and off-pump coronary artery bypass surgery.

Methods: From 1997 to 2000, primary coronary artery bypass grafting was performed in 481 patients off pump and in 3231 patients on pump. Hospital outcomes were compared between propensity-matched pairs of 406 on-pump and 406 off-pump patients. The 2 groups were similar in age ($P = .9$), left ventricular function ($P = .7$), extent of coronary artery disease ($P = .5$), carotid artery disease ($P = .4$), and chronic obstructive pulmonary disease ($P = .5$). However, off-pump patients had more previous strokes ($P = .05$) and peripheral vascular disease ($P = .02$); on-pump patients had a higher preoperative New York Heart Association class ($P = .01$).

Results: In the matched pairs the mean number of bypass grafts was 2.8 ± 1.0 in off-pump patients and 3.5 ± 1.1 in on-pump patients ($P < .001$). Fewer grafts were performed to the circumflex ($P < .001$) and right coronary ($P = .006$) artery systems in the off-pump patients. Postoperative mortality, stroke, myocardial infarction, and reoperation for bleeding were similar in the 2 groups. There was more encephalopathy ($P = .02$), sternal wound infection ($P = .04$), red blood cell use ($P = .002$), and renal failure requiring dialysis ($P = .03$) in the on-pump patients.

Conclusions: Both off- and on-pump procedures produced excellent early clinical results with low mortality. An advantage of an off-pump operation was less postoperative morbidity; however, less complete revascularization introduced uncertainty about late results. A disadvantage of on-pump bypass was higher morbidity that seemed attributable to cardiopulmonary bypass.

Cardiac surgeons have readopted off-pump coronary artery bypass surgery to decrease the morbidity and mortality of myocardial revascularization. However, does off-pump surgery truly reduce morbidity and mortality? Some clinical studies appear to indicate that it does.¹⁻⁶ This issue remains unresolved, however, because characteristics of on- and off-pump patient groups are dissimilar in these studies. At present, no randomized studies address this issue.

To reduce the effect of selection bias, we have compared outcomes of on- and off-pump coronary artery bypass surgery in propensity-matched pairs. Using this technique, we analyzed patients who were equally likely to be treated with on- or

off-pump surgery and excluded patients from the analysis if there was a high likelihood of using only one of the revascularization strategies.

Patients and Methods

Patients

From January 1997 through June 2000, 3712 patients underwent primary coronary artery bypass surgery at The Cleveland Clinic Foundation. At the discretion of the operating surgeon, myocardial revascularization was performed off pump in 481 patients and with cardiopulmonary bypass (CPB) in 3231 patients. On- and off-pump patients were contemporaneous and not sequential groups; however, the number of off-pump coronary artery bypass operations increased during this period.

All patients included in the study underwent revascularization through a median sternotomy. Patients undergoing coronary reoperations, combined operations, or coronary revascularization through a thoracotomy were excluded. However, patients who were converted from off-pump to on-pump bypass were retained ($n = 15$); thus, this represents an intent-to-treat study.

Methods

Surgical technique: Off pump. All operations were performed through a median sternotomy. Conduits were harvested and prepared, and patients were heparinized. Patients were placed in the Trendelenburg position and rotated to the right to assist in coronary artery exposure and prevent hemodynamic instability during construction of the distal anastomoses.

Our technique of coronary artery exposure evolved during this study. Early in our experience, 4 slings (2 through the transverse sinus and 2 behind the inferior vena cava) were manipulated to expose the coronary arteries. For most of the study, 2 to 4 deep pericardial sutures were placed in the posterior pericardium, at the level of the left superior and inferior pulmonary veins, and between the left inferior pulmonary vein and inferior vena cava. Traction on these sutures elevated and rotated the heart to the right and exposed the lateral, posterior, and inferior coronary arteries.

Commercially available mechanical stabilizers were used to perform distal anastomoses. During construction of these anastomoses, target vessel hemostasis was obtained with intravascular shunts, a proximal loop, or proximal and distal vessel loops. A humidified carbon dioxide blower was used.

Distal anastomoses were usually constructed before proximal anastomoses. The left internal thoracic artery to left anterior descending coronary artery anastomosis was constructed first. Proximal anastomoses were constructed to the aorta with a tangential clamp. After completion of all anastomoses, heparin was reversed, and aspirin was given 8 hours postoperatively.

Surgical technique: On pump. All operations were performed through a median sternotomy. Conduits were harvested and prepared, and patients were heparinized. Standard cannulation for CPB was performed with ascending aortic cannulation and dual-stage cannulation of the right atrium. Both antegrade and retrograde cardioplegia cannulas were placed.

Although there were some minor differences in CPB routine among surgeons, for the most part, the procedure was conducted as follows. Arterial flow was adjusted to 2.0 to $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, and blood pressure was maintained between 50 and 70 mm Hg.

The aorta was crossclamped, and cold blood cardioplegia was administered either antegrade or retrograde or in combination on induction and every 15 minutes. Patients' temperatures were either kept warm or allowed to drift to 34°C during CPB.

Distal anastomoses were usually constructed first, and the proximal anastomoses were constructed to the ascending aorta during a single crossclamp period, thus eliminating the need for tangential and multiple clampings of the aorta. After the patient was weaned from CPB and decannulated, heparin was reversed, and aspirin was administered 8 hours postoperatively.

Data Collection

Patients were identified from the prospective computerized Cardiovascular Information Registry, and preoperative, operative, and postoperative variables (Appendix Table 1) were retrieved from this database and 2 other computerized databases whose use for research has been approved by The Cleveland Clinic Foundation Institutional Review Board.

Identifying the Influence of Selection

Patients operated on off pump differed in many clinical characteristics from on-pump patients. Off-pump patients were older than on-pump patients (66 ± 11.3 vs 64 ± 10.4 years, $P < .001$), more likely to be women (32% vs 25%, $P = .001$), less likely to have insulin-treated diabetes (10% vs 14%, $P = .05$), and more likely to have carotid artery disease (22% vs 14%, $P < .001$), peripheral vascular disease (18% vs 13%, $P = .009$), hypertension (75% vs 70%, $P = .03$), and renal disease (3.7% vs 1.1%, $P < .001$). They were less symptomatic (in New York Heart Association class IV: 17% vs 29%, $P < .001$) and had less extensive coronary artery disease (3-system disease: 53% vs 72%, $P < .001$).

To reduce the influence of selection on the comparison of outcome, we used propensity-score pairwise matching of off-pump patients to the pool of available on-pump patients.^{7,8} This was a 2-step process. First, using known preoperative variables (Appendix Table 1) and multivariable logistic regression, we determined the factors associated with on- versus off-pump bypass (group membership). We initially analyzed the continuous and ordinal variables by means of decile analysis, selecting those transformations of scale that best calibrated the variable to group membership.

Variable selection, with a P value criterion for retention of variables in the model of .05, used bootstrap bagging.⁹ This was a 4-step process. First, a patient was randomly selected from the original data set to begin a new data set. The original data set continued to be sampled until the new data set was 75% of the size of the original. Second, risk factors were identified with automated forward stepwise selection. Third, results of the variable selection were stored. These 3 steps were repeated 200 times. Finally, the frequency of occurrence of variables related to group membership was ascertained and indicated the reliability of each variable.⁹ In addition, a guided analysis was performed of the original data set.¹⁰ All variables with bootstrap reliability of 50% or greater were also in the guided analysis, but 2 variables identified by guided analysis, history of hypertension and insulin-treated diabetes, appeared in only 40% and 42% of bootstrap samples, respectively.

TABLE 1. Comparison of patient characteristics in propensity-matched pairs

Characteristics	On pump (n = 406)	Off pump (n = 406)	P value
Demography			
Age (mean $\pm$ SD)	66 $\pm$ 11.3	66 $\pm$ 11	.9*
Male	284 (70)†	280 (69)	.8
Noncardiac			
Diabetes			
Insulin treated	35 (8.6)	44 (11)	.3
Oral hypoglycemics	80 (20)	76 (19)	.7
Previous stroke	23 (5.7)	38 (9.4)	.05
Carotid disease	79 (19)	88 (22)	.4
Peripheral vascular disease	50 (12)	74 (18)	.02
Smoking history	258 (64)	162 (65)	.7
Chronic obstructive pulmonary disease	78 (19)	60 (21)	.5
Hypertension	295 (73)	300 (74)	.7
Renal disease	10 (2.5)	4 (1.0)	.1
NYHA class			.01
I	29 (7.2)	28 (9.9)	
II	201 (50)	144 (51)	
III	62 (15)	61 (21)	
IV	111 (28)	51 (18)	
Not recorded	3	122	
Left ventricular dysfunction			.6
Normal/none	252 (62)	245 (63)	
Mild	81 (20)	77 (20)	
Moderate	38 (9.4)	43 (11)	
Severe	33 (8.2)	24 (6.2)	
Not recorded	2	17	
History of myocardial infarction	203 (50)	205 (50)	.9
Coronary artery disease ($\geq$ 50%)			
Left main	93 (23)	91 (22)	.9
LAD	366 (90)	373 (92)	.4
LCX	289 (71)	279 (69)	.5
RCA	315 (78)	315 (78)	1.0
No. of diseased systems‡			.5
0	1 (0.2)§	0 (0)	
1	34 (8.4)	42 (10)	
2	119 (29)	124 (31)	
3	252 (62)	240 (59)	

LAD, Left anterior descending coronary artery system; LCX, left circumflex coronary artery system; RCA, right coronary artery system.

*Wilcoxon rank sum test.

†Presented as number (% of column total).

‡Defined as 50% lesion in the coronary system; left main disease is defined by itself and is not coded as 2-system disease.

§In one patient there was 40% left main disease and 30% LAD disease.

Having established a parsimonious model (Appendix Table 2), we added other variables representing groups of patient and coronary disease factors that might be related to unrecorded selection factors (saturated model). These variables were sex, body mass index to represent patient size variables, left ventricular function, history of arrhythmias (atrial fibrillation, ventricular fibrillation, and ventricular tachycardia), smoking history, peripheral vascular disease, chronic obstructive pulmonary disease, previous stroke, left main disease, and left anterior descending coronary artery disease. The C statistic was .72.

A propensity score was calculated for each patient by solving the saturated model for the probability of off-pump bypass. Using only the propensity score, on-pump patients were matched to off-pump patients by using a greedy matching strategy.¹¹ For this, matching to 5 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 406 off-pump patients propensity matched to 406 on-pump patients.

Outcomes

In-hospital outcomes were recorded by respiratory therapists dedicated to recording postoperative complications occurring in the intensive care unit and by experienced nurses also dedicated to collecting patient information, operative details, and in-hospital complications. Operative details were collected within 48 hours of the operation.

Operative variables compared included bypass conduits, number and site of distal anastomoses, and completeness of revascularization. Incomplete revascularization was defined as lack of grafting into any system with 50% or more lesions or failure to graft into both the left anterior descending and circumflex systems for 50% or greater left main trunk disease.

Postoperative events, identified according to definitions of the Society of Thoracic Surgeons for Version 2.35 of the Adult Cardiac Surgery Database (see National Databases for details, www.sts.org) included hospital death, stroke, encephalopathy (as determined by a staff neurologist), myocardial infarction, reoperation for bleeding, red blood cell use, sternal wound infection, renal failure requiring dialysis, acute respiratory distress syndrome, pancreatitis, and gastrointestinal bleeding.

Direct technical cost data, exclusive of professional salaries, were obtained from the Transaction Systems Incorporated cost accounting system (Eclipsys Corporation, Boston, Mass). Because of Cleveland Clinic policy, financial data are presented by relative statistics only.

Comparison of Outcomes

Outcomes were compared between the 2 propensity-matched groups of patients. We also compared the outcomes in 75 unmatched off-pump patients with those matched.

These comparisons were supplemented by 2 other methods of using the propensity score: quintile substratification analysis and multivariable adjustment. The results were entirely consistent with the matched-pairs analysis and are not shown.

Results

Effectiveness of Matching

Preoperative characteristics of on- and off-pump propensity-matched patients were well matched, including similar extent of coronary artery disease (Table 1). Off-pump patients had more peripheral vascular disease and history of stroke and were somewhat less symptomatic. These were the only dissimilar characteristics ($P \leq .05$) among 70 examined.

Comparison of Revascularization

Despite having similar extent of coronary artery disease, more bypass grafts were performed per patient in on-pump

TABLE 2. Comparison of coronary bypass procedures in propensity-matched pairs

Procedure	On pump (n = 406)	Off pump (n = 406)	P value
No. of distal anastomoses (mean ± SD)	3.5 ± 1.12	2.8 ± 1.04	<.001*
Percentage performed with arterial grafts	53 ± 33	64 ± 30	<.001
Coronary systems grafted			
LAD	391 (96)†	390 (96)	.8
LCX	336 (82)	263 (65)	<.001
RCA	289 (70)	252 (62)	.006
Diagonal	195 (48)	169 (42)	.05
Conduits used			
LITA	371 (91)	382 (94)	.1
RITA	80 (20)	47 (12)	.001
Radial artery	144 (36)	190 (47)	.001
Saphenous vein	320 (79)	271 (67)	<.001
Incomplete revascularization	74 (18)	125 (31)	<.001

LAD, Left anterior descending coronary artery system; LCX, left circumflex coronary artery system; RCA, right coronary artery system; LITA, left internal thoracic artery; RITA, right internal thoracic artery.

*Wilcoxon rank sum test.

†Presented as number (% of column total).

patients (Table 2). Fewer bypass grafts were performed to the circumflex and right coronary artery systems in the off-pump group. Incomplete revascularization was higher in off-pump patients. In 68% of patients, the reason for incomplete revascularization was stated by the surgeon, but in the remaining patients, no reason was given (Table 3). Arterial grafts were used in a higher proportion of the distal anastomoses in off-pump patients. Left internal thoracic artery grafting was similar; however, the off-pump group had less right internal thoracic artery and saphenous vein bypass grafting and more radial artery bypass grafting.

Comparison of Postoperative Events

Hospital death, stroke, and myocardial infarction were similar in the on- and off-pump patients (Table 4). However, off-pump patients experienced less encephalopathy, renal failure requiring dialysis, and red blood cell use and fewer sternal wound infections.

Comparing Costs

Hospital direct technical costs were 13% greater in off-pump patients (Table 5). Most of this increase was due to higher operating room costs, which includes nursing labor and surgical disposables. For both on- and off-pump patients, the median intensive care unit stay and postoperative length of stay were 1 and 6 days, respectively.

Unmatched Off-Pump Patients

There were important differences in patient characteristics, revascularization, and outcomes in the matched and un-

TABLE 3. Reasons for incomplete revascularization

Reason	On pump		Off pump	
	No.	% of 406	No.	% of 406
Coronary artery thought unsuitable for grafting	41	10.1	48	11.8
Infarcted/scarred myocardium	4	1.0	16	3.9
Coronary artery unsuitable and myocardium infarcted/scarred	1	0.2	7	1.7
Circumflex artery not grafted in left main disease	4	1.0	7	1.7
Hemodynamic instability	0	0	4	1.0
Diagonal grafted instead of LAD	2	0.5	0	0
Not given	22	5.4	43	10.6
Total	74	18	125	31

P = .03 (χ^2 test) for difference between on- and off-pump distribution of reasons.

LAD, Left anterior descending coronary artery.

TABLE 4. Comparison of postoperative events in propensity-matched pairs

Event	On pump (n = 406)	Off pump (n = 406)	P value
Hospital mortality	4 (1.0)*	2 (0.5)	.7
Stroke	5 (1.2)	3 (0.7)	.7
Encephalopathy	7 (1.7)	0 (0.0)	.02
Myocardial infarction	5 (1.2)	3 (0.7)	.7
Reoperation for bleeding	10 (2.5)	7 (1.7)	.5
Deep sternal wound infection	8 (2.0)	1 (0.2)	.04
Dialysis	6 (1.5)	0 (0.0)	.03
ARDS	1 (0.2)	0 (0.0)	1.0
Gastrointestinal bleeding	2 (0.5)	2 (0.5)	1.0
Pancreatitis	0 (0.0)	1 (0.2)	1.0
Red cell transfusion	214 (53)	169 (42)	.002

ARDS, Acute respiratory distress syndrome.

*Presented as number (% of column total).

matched off-pump patients (Table 6). Unmatched off-pump patients had more preoperative renal failure, less extensive coronary artery disease, fewer bypass grafts, and higher mortality. Evidence of increasing systematic selection of patients for off-pump operation is that the proportion of unmatched patients increased over time (Figure 1). The patients included, for example, the extremes of age (Figure 2), extremes of creatinine levels, and more comorbidities (Table 7).

Discussion

Background

Technological advances in CPB and myocardial protection led to almost complete abandonment of myocardial revascularization performed off pump. These techniques allow coronary artery bypass surgery to be performed in a quiet,

TABLE 5. Relative direct technical costs from day of operation to hospital discharge in propensity-matched pairs

Cost component	% of total median on-pump cost	% difference between on- and off-pump median costs*	P value†
Operating room	26	44	<.001
Anesthesia	15	−5.9	.02
Perfusion	14	−26	<.001
ICU	11	1.9	.02
Postoperative floor	16	−8.8	.001
Radiology	0.9	8.3	.003
Pharmacy	5.8	9.1	.04
Clinical laboratory	4.4	−31	<.001
Medical tests	2.6	−0.6	.4
Total	100‡	13	<.001

ICU, Intensive care unit.

*[(Median off pump − Median on pump)/Mean on pump].

†Wilcoxon rank sum test.

‡Sum of listed components does not add up to 100% because the components are median relative values (%).

TABLE 6. Statistically significant differences between unmatched and propensity-matched off-pump patients

Variables and events	Unmatched (n = 75)	Matched (n = 406)	P value
Patient characteristics			
Renal disease	14 (19)*	4 (1.0)	<.001
Left ventricular dysfunction			.04
Normal/none	46 (71)	245 (63)	
Mild	5 (7.7)	77 (20)	
Moderate	6 (9.2)	43 (11)	
Severe	8 (12)	24 (6.2)	
Not recorded	10	17	
Coronary artery disease (≥50%)			
LCX	36 (48)	279 (69)	<.001
RCA	27 (36)	315 (78)	<.001
No. of diseased systems			<.001
1	21 (28)	42 (10)	
2	38 (51)	124 (31)	
3	16 (21)	240 (59)	
Surgical outcomes			
No. of distal anastomoses (mean ± SD)	2.4 ± 0.94	2.8 ± 1.04	<.001
RCA grafted	29 (39)	252 (62)	<.001
LCX grafted	39 (52)	263 (65)	.04
Postoperative events			
Hospital death	5 (6.7)	2 (0.5)	.001

LAD, Left anterior descending coronary artery system; LCX, left circumflex coronary artery system; RCA, right coronary artery system.

*Presented as number (% of column total).

bloodless field. This resulted in not only widespread adoption and application of coronary artery bypass surgery but also highly reproducible and excellent short- and long-term outcomes.

However, in recent years, the deleterious effects of CPB and aortic manipulation have become well known. Therefore, surgeons have attempted to reduce even further the morbidity of cardiac operations by turning once again to off-pump coronary artery bypass. The renewed interest in off-pump myocardial revascularization has generated technological advances that have improved methods of coronary artery stabilization and exposure, allowing access to all coronary arteries and complete revascularization.

Challenges of Comparison

Off-pump coronary artery bypass surgery is now possible, but is it better? Multiple clinical studies have examined this question without arriving at a consensus. The problems are twofold. First, both on- and off-pump strategies yield good outcomes in experienced centers. Second, patient selection has had a large confounding effect on comparisons. The best way to eliminate bias is to perform a randomized trial. However, in this setting, with very low occurrence of postoperative events with on-pump coronary artery bypass surgery, a randomized study would require thousands of patients.

The standards of randomized trials can be achieved partially with clinical studies such as this one, by matching patients to obtain comparable groups. In this study we used propensity-score matching.^{7,8,11}

Principal Findings

Death, stroke, and myocardial infarction. Hospital mortality, stroke, and myocardial infarction were similar in the propensity-matched pairs. The risk of each of these events with both revascularization strategies was low, about 1% (Appendix Table 3). Other clinical studies have likewise demonstrated no clear superiority in terms of mortality, stroke, or myocardial infarction when comparing on- and off-pump surgical strategies.¹²⁻¹⁶

In unmatched off-pump patients, mortality was higher. This group of patients was selected for off-pump surgery because they were believed to be too high risk for CPB. Compared with on-pump patients, these patients were either very old or very young, had a large body mass index, had more preoperative renal failure, had a more recent operation, and had less extensive coronary artery disease. We believe risk factors accounted for higher mortality in these patients.

Encephalopathy, red cell transfusion, sternal wound infection, and dialysis. There was more postoperative morbidity in the on-pump patients. Encephalopathy, red blood cell transfusions, sternal wound infections, and renal failure requiring dialysis were all more common. We believe these morbidities in the on-pump patients can be attributed directly to CPB.

Neurocognitive impairment after CPB, reflected in this study by encephalopathy, is believed to be due to microem-

Figure 1. Within the off-pump group, percentage of patients unmatched to an on-pump counterpart according to year of off-pump operation.

Figure 2. Within the off-pump group, percentage of patients unmatched to an on-pump counterpart according to age.

boli, nonphysiologic perfusion, and the inflammatory response.¹⁷ These result in neuronal injury, increased permeability of the blood-brain barrier, and cerebral edema.¹⁸ Studies have demonstrated increased levels of the biochemical marker for neuronal injury, S100 β , after on-pump surgery, with no significant increase after off-pump surgery.^{19,20} However, the long-term importance of the neurocognitive changes and S100 β elevations after CPB is unknown. Some studies suggest that these neurocognitive

deficits might be transient and resolve several months after the operation,^{17,21-23} whereas a recent study by Newman and colleagues²⁴ suggests that patients exhibiting neurocognitive dysfunction after CPB are at risk for long-term neurocognitive dysfunction.

Our study might have underestimated the neurocognitive benefit of off-pump surgery. We measured encephalopathy, a clinically apparent event. Because much of the neurocognitive impairment after CPB is subtle, extensive preopera-

TABLE 7. Factors associated with inability to match off-pump with on-pump patients

Factor	Logistic coefficient $\pm$ SE	P value
Old age*	3.9 $\pm$ 1.46	.008
Young age	-0.25 $\pm$ 0.109	.03
Large BMI	0.057 $\pm$ 0.027	.04
Renal disease	5.2 $\pm$ 0.79	<.0001
More recent operation	0.123 $\pm$ 0.023	<.0001
More extensive coronary disease††	-2.5 $\pm$ 0.77	.001
Any RCA disease‡	-1.78 $\pm$ 0.42	<.0001
Any LCX disease‡	-1.58 $\pm$ 0.45	.0005
Intercept	-1.19	

C statistic = .94.

BMI, Body mass index; RCA, right coronary artery system; LCX, left circumflex coronary artery system.

*exp[age/50] natural exponential transformation.

†ln[number of diseased systems $\geq$ 50%-1] natural logarithmic transformation.

‡The negative sign indicates that these characteristics are associated with greater ability to match.

tive and postoperative neurocognitive testing is required to detect a postoperative decrement. A limitation of our study is that these tests were not performed.

Findings of increased red blood cell transfusions in on-pump versus off-pump patients, similar to our own results, were recently reported by Ascione and coworkers.²⁵ They demonstrated increased red blood cell loss and higher red blood cell, platelet, and fresh frozen plasma transfusions in on-pump patients. CPB can lead to increased red blood cell transfusion requirement in multiple ways. Surface activation of platelets and coagulation proteins during CPB results in platelet dysfunction and coagulopathy, leading to postoperative bleeding.^{26,27} The crystalloid solutions needed to prime the pump result in hemodilution, and the turbulence, cavitation, and osmotic stresses during CPB result in red blood cell membrane injury and hemolysis.

Renal injury during CPB might be due to altered renal perfusion during periods of hypotension or low flow, vasoconstrictors, or microemboli. Hemoglobinuria, as a result of hemolysis during CPB, might also lead to renal dysfunction.

CPB has multiple effects depressing the immunologic system. Complement activation resulting in complement factor depletion, lymphopenia, and natural killer cell impairment and pulmonary sequestrations of polymorphonuclear leukocytes and neutropenia have been shown to occur after CPB.^{28,29} These might result in increased susceptibility to infections and explain our finding of increased sternal wound infections in on-pump patients.

Incomplete revascularization. A worrisome finding in our study was more incomplete revascularization in the off-pump patients. When the reasons for incomplete revascularization were given, they were similar in patients un-

dergoing on- and off-pump bypass. The difference in incomplete revascularization occurred primarily in patients in whom the reason could not be determined, and only rarely for hemodynamic instability unique to off-pump revascularization. Although incomplete revascularization did not increase early risk, it might affect the long-term results of off-pump revascularization.³⁰⁻³² Arom and colleagues¹⁶ found that at 1 year after the operation, off-pump patients had a higher risk of recurrent angina and reinterventional procedures compared with on-pump patients. Similar to our findings, the off-pump patients in their study received fewer bypass grafts than did the on-pump patients.

Cost. Total direct technical costs were increased in the off-pump patients. Much of this increase occurred in the operating room as a result of longer procedures and disposable stabilizers. Perfusion costs, as expected, were less in the off-pump patients, but this did not compensate for the increase in other operating room costs. There were only minor differences in intensive care unit and floor costs.

Does Off-Pump Surgery Reduce Mortality and Morbidity?

The results of both on- and off-pump myocardial revascularization are excellent, with low risk of death, stroke, and myocardial infarction. The procedures, however, are not equivalent and appear to have different risks. On-pump surgery is associated with higher morbidity, which can be attributed directly to CPB. Thus, an advantage of off-pump revascularization is lower postoperative morbidity. However, there is more incomplete revascularization in off-pump surgery, and this might be a future disadvantage.

We thank Daniel Karchmere for his assistance with the direct technical costs comparison and Tess Knerik for manuscript preparation.

References

1. Puskas JD, Wright CE, Ronson RS, Brown WM, Gott JP, Guyton RA. Off-pump multivessel coronary bypass via sternotomy is safe and effective. *Ann Thorac Surg.* 1998;66:1068-72.
2. Koutlas TC, Elbeery JR, Williams JM, Moran JF, Francalancia NA, Chitwood WR Jr. Myocardial revascularization in the elderly using beating heart coronary artery bypass surgery. *Ann Thorac Surg.* 2000;69:1042-7.
3. Yokoyama T, Baumgartner FJ, Gheissari A, Capouya ER, Panagiotides GP, Declusin RJ. Off-pump versus on-pump coronary bypass in high-risk subgroups. *Ann Thorac Surg.* 2000;70:1546-50.
4. Iaco AL, Contini M, Teodori G, Di Mauro M, Di Giammarco G, Vitolla G, et al. Off or on bypass: what is the safety threshold? *Ann Thorac Surg.* 1999;68:1486-9.
5. Calafiore AM, Teodori G, Di Giammarco G, Vitolla G, Maddestra N, Paloscia L, et al. Multiple arterial conduits without cardiopulmonary bypass: early angiographic results. *Ann Thorac Surg.* 1999;67:450-6.
6. Buffolo E, Silva de Andrade JC, Rodrigues Branco JN, Teles CA, Aguiar LF, Gomes WJ. Coronary artery bypass grafting without cardiopulmonary bypass. *Ann Thorac Surg.* 1996;61:63-6.
7. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70:41-55.

8. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265-81.
9. Breiman L. Bagging predictors. *Machine Learning*. 1996;24:123-40.
10. Baskerville JC, Toogood JH. Guided regression modeling for prediction and exploration of structure with many explanatory variables. *Technometrics*. 1982;24:9-17.
11. Parsons LS. Reducing bias in propensity score matched-pair sample using greedy matching techniques. In: Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference, Long Beach, Calif. Cary, NC: SAS Institute Inc; 2001.
12. Contini M, Iaco A, Iovino T, Teodori G, Di Giammarco G, Mazzei V, et al. Current results in off pump surgery. *Eur J Cardiothorac Surg*. 1999;16:S69-72.
13. Bull DA, Neumayer LA, Stringham JC, Meldrum P, Affleck DG, Karwande SV. Coronary artery bypass grafting with cardiopulmonary bypass versus off-pump cardiopulmonary bypass grafting: does eliminating the pump reduce morbidity and cost? *Ann Thorac Surg*. 2001;71:170-5.
14. Kshetry VR, Flavin TF, Emery RW, Nicoloff DM, Arom KV, Petersen RJ. Does multivessel, off-pump coronary artery bypass reduce postoperative morbidity? *Ann Thorac Surg*. 2000;69:1725-30.
15. Czemy M, Baumer H, Kilo J, Zuckermann A, Grubhofer G, Chevtchik O, et al. Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. *Ann Thorac Surg*. 2001;71:165-9.
16. Arom KV, Flavin TF, Emery RW, Kshetry VR, Janey PA, Petersen RJ. Safety and efficacy of off-pump coronary artery bypass grafting. *Ann Thorac Surg*. 2000;69:704-10.
17. Westaby S, Johnsson P, Parry AJ, Blomqvist S, Solem JO, Ailing C, et al. Serum S100 protein: a potential marker for cerebral events during cardiopulmonary bypass. *Ann Thorac Surg*. 1996;61:88-92.
18. Anderson RE, Li TQ, Hindmarch T, Settergren G, Vaage J. Increased extracellular brain water after coronary artery bypass grafting is avoided by off-pump surgery. *J Cardiothorac Vasc Anesth*. 1999;13:698-702.
19. Lloyd CT, Ascione R, Underwood MJ, Gardner F, Black A, Angelini GD. Serum S-100 protein release and neuropsychologic outcome during coronary revascularization on the beating heart: a prospective randomized study. *J Thorac Cardiovasc Surg*. 2000;119:148-54.
20. Wandschneider W, Thalmann M, Trampitsch E, Ziervogel G, Kobinia G. Off-pump coronary bypass operations significantly reduce S100 release: an indicator for less cerebral damage? *Ann Thorac Surg*. 2000;70:1577-9.
21. Taggart DP, Browne SM, Halligan PW, Wade DT. Is cardiopulmonary bypass still the cause of cognitive dysfunction after cardiac operations? *J Thorac Cardiovasc Surg*. 1999;118:420-1.
22. Vingerhoets G, Jannes C, De Soete G, Van Nooten G. Prospective evaluation of verbal memory performance after cardiopulmonary bypass surgery. *J Clin Exp Neuropsychol*. 1996;18:187-96.
23. Toner I, Taylor KM, Newman S, Smith PL. Cerebral functional changes following cardiac surgery: neuropsychological and EEG assessment. *Eur J Cardiothorac Surg*. 1998;13:13-20.
24. Newman MF, Kirchner JL, Phillips-Bute B, Gaver B, Grocott H, Jones RH, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med*. 2001;344:395-402.
25. Ascione R, Williams S, Lloyd CT. Reduced postoperative blood loss and transfusion requirement after beating-heart coronary operations: a prospective randomized study. *J Thorac Cardiovasc Surg*. 2001;121:689-96.
26. Kawahito K, Kobayashi E, Iwasa H, Misawa Y, Fuse K. Platelet aggregation during cardiopulmonary bypass evaluated by a laser light-scattering method. *Ann Thorac Surg*. 1999;69:79-84.
27. Kestin AS, Valeri CR, Khuri SF, Loscalzo J, Ellis PA, MacGregor H, et al. The platelet function defect of cardiopulmonary bypass. *Blood*. 1993;82:107-17.
28. Chiu RC, Samson R. Complement (C3, C4) consumption in cardiopulmonary bypass, cardioplegia, and protamine administration. *Ann Thorac Surg*. 1984;37:229-32.
29. Hamano K, Gohra H, Katoh T, Fujimura Y, Zempo N, Esato K. The preoperative administration of lentian ameliorated the impairment of natural killer activity after cardiopulmonary bypass. *Int J Immunopharmacol*. 1999;21:531-40.
30. Scott R, Blackstone EH, McCarthy PM, Lytle BW, Loop FD, White JA, et al. 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.
31. Bell MR, Gersh BJ, Schaff HV, Holmes DR Jr, Fischer LD, Alderman EL, et al. 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.
32. Jones EL, Weintraub WS. The importance of completeness of revascularization during long-term follow-up after coronary artery bypass operations. *J Thorac Cardiovasc Surg*. 1996;112:227-37.

APPENDIX TABLE 1. Patient variables considered in analyses

Demography
Age, sex, height, weight, body surface area, body mass index, weight/height ratio
Symptoms
Functional class (highest angina or functional limitation, I-IV)
Left ventricular function
Left ventricular dysfunction grade (none, mildly, moderately, or severely impaired), history of prior myocardial infarction, chronic heart failure
Cardiac comorbidity
Atrial fibrillation, ventricular tachycardia, use of intra-aortic balloon counterpulsation preoperatively
Noncardiac comorbidity
Smoking history, carotid artery disease, history of stroke, peripheral vascular disease, hypertension, diabetes (insulin treated, oral hypoglycemic), renal disease by history, chronic obstructive pulmonary disease
Coronary disease
Degree of stenosis in left main trunk, left anterior descending coronary artery system, right coronary artery stem, circumflex artery system, number of diseased systems
Preoperative laboratory data
Hematocrit, creatinine
Interactive terms
Age and diabetes

APPENDIX TABLE 2. Factors associated with propensity to use on- and off-pump techniques

Off-pump variable	P value	On-pump variable	P value
Old age	.0006	Higher NYHA class	.0003
Young age	.0004	Preoperative IABP	.03
Creatinine >2	<.0001	Diabetes	.03
High creatinine	.04	High hematocrit	.0003
Low creatinine	.001	More extensive CAD	.0002
Carotid disease	.001	RCA stenosis	<.0001
Hypertension	.04	LCX stenosis	<.0001

NYHA, New York Heart Association; IABP, intra-aortic balloon pump; CAD, coronary artery disease; RCA, right coronary artery system; LCX, left circumflex artery system.

APPENDIX TABLE 3. Comparison of postoperative events in entire group

Event	On pump (n = 3231)	Off pump (n = 481)	P value
Hospital mortality	31 (1.0)*	7 (1.5)	.3
Stroke	44 (1.4)	4 (0.8)	.3
Encephalopathy	44 (1.4)	1 (0.2)	.3
Myocardial infarction	29 (0.9)	4 (0.8)	1.0
Reoperation for bleeding	73 (2.3)	9 (1.9)	.6
Deep sternal wound infection	63 (1.9)	2 (0.4)	.02
Dialysis	35 (1.1)	1 (0.2)	.08
ARDS	17 (0.5)	0 (0.0)	.2
Gastrointestinal bleeding	20 (0.6)	4 (0.8)	.5
Pancreatitis	6 (0.2)	1 (0.2)	1.0
Red cell transfusion	1481 (46)	210 (42)	.1

ARDS, Acute respiratory distress syndrome.

*Presented as number (% of column total).

Discussion

Dr Lawrence Cohn (*Brookline, Mass*). Dr Sabik, that was a beautifully organized article, and you presented it very well. I can say that, because Dr Sabik worked in my laboratory as a Harvard medical student, and he did an excellent job there.

I think this is the best attempt so far to compare off-pump with on-pump coronary artery bypass grafting, and you have done a very nice job, short, of course, of randomization, which is yet to be done.

I did want to point out one thing. Your abstract is a declarative sentence, but the manuscript that you sent me and your introductory slide presented a question, and the data are slightly different. Could you clarify this when you discuss these questions?

I read all 55 pages of your manuscript, including the 15-page appendix. Obviously Dr Blackstone's touch is here, and like every surgeon that presents a new technique, every couple of years Dr Blackstone presents to us a new concept in statistical treatment, which obviously adds greatly to our knowledge. Propensity matching is excellent because it more carefully allows us to match patients.

Overall, in this 5-way analysis, off-pump grafting shows underrevascularization. In the old days, the 1980s and 1990s, we thought that complete revascularization was a bedrock of coronary bypass. Do you have a sense of how this is going to play out, or are these patients generally at such high risk that that is not really going to become a factor in the long term because these patients might not survive for other reasons?

With your analysis, you did show that the early events—encephalopathy, renal failure, wound infection, red cell transfusions—are better in the off-pump group. Encephalopathy is a very controversial area. Some of us took exception to a recent article in *The New England Journal of Medicine* because it was not matched according to age. Do you have a concept that the encephalopathy you saw in both groups was correlated with age? At Brigham, we noticed a remarkable decrease in encephalopathy and stroke, especially in patients older than 70 years of age, when we reverted to the single-clamp technique for coronary bypass about 10 years ago.

You noted that the cost is 13% greater with off-pump bypass grafting. Unlike other studies that purport to say that, you can do an off-pump graft and the patient goes home the next day, and you

had exactly the same intensive care unit and hospital stay. You mentioned the costs being higher with off-pump grafting. Can you explain why that might be?

Finally, and you did not have a chance to go into it because it is such a complete statistical treatment of these data, in the highest risk quintiles of the propensity matching, the fourth and fifth quintiles, the operative mortality in the off-pump group is higher than in those patients who were treated with coronary artery bypass grafting on bypass. This raises an interesting paradox. On our service, we often use off-pump grafting in the highest risk patients, trying to decrease these encephalopathic findings, renal failure, et cetera, but are we trading a slightly lower incidence of encephalopathy for higher operative risk?

Finally, on the basis of these data, should we expand our indications for off-pump grafting, or should we continue to restrict our indications to the highest risk patients?

Dr Sabik. Thank you, Dr Cohn, for your kind and thoughtful remarks. The reason that the abstract we submitted is a little different from this presentation and the paper is that we slightly changed the patient population and statistical methods of the study. We believe these changes improved this study by improving our ability to match the off-pump and on-pump patients. The first change we made was to remove patients undergoing reoperations. We believe it is important to match the on- and off-pump patients in terms of the extent of coronary artery disease. Patients who are having coronary reoperations have both patent vein grafts and diseased native vessels, and this makes it difficult to classify them as to whether they have single-, double-, or triple-vessel disease. Therefore, to match the patients in regard to the extent of coronary artery disease, those who underwent reoperations were removed.

Our second change was to rematch the patients using a new statistical method involving propensity scores. This technique, called greedy matching, was not known to us at the time we submitted this abstract. With this technique, propensity scores are used to do one to one matching. We were able to improve on the matching of the on-pump and off-pump patients and obtain 2 groups of patients with very similar preoperative characteristics. Despite having changed the methods of the study slightly, I do not believe that our conclusions have changed significantly. Mortality and the major morbidities of stroke and myocardial infarction remained similar in the on-pump and off-pump patients. Our belief, from the conclusions of the first abstract, was that the benefits of off-pump surgery were related to the elimination of the transient effects associated with CPB. By improving the matching, I believe we were better able to demonstrate this. The complications that can be related directly to CPB, such as coagulopathy, immunosuppression, and brain edema, led to more morbidity in the on-pump patients, such as more red blood cell transfusions, more sternal wound infections, and more encephalopathy. Therefore, we believe that by improving the matching, we were able to strengthen the conclusions of our original abstract. Because we were able to identify more morbidity in the on-pump patients, we changed the title from a declarative statement to a question.

I do not know how the increased occurrence of incomplete revascularization in the off-pump patients will play out over time. In this study incomplete revascularization did not increase the early risk in the off-pump patients, but it might increase the late risk. If the risk of CPB is greater than the risk associated with incomplete

revascularization in high-risk patients, then off-pump surgery with incomplete revascularization might be beneficial in these patients. We will have to follow up these patients and determine the effect, if any, of incomplete revascularization over time.

In the propensity-matched groups there were too few patients with the postoperative complication of encephalopathy to determine its preoperative risk factors. However, in the entire group of on-pump patients, there were enough individuals with postoperative encephalopathy to determine some preoperative risk factors. These include high preoperative creatinine, preoperative atrial fibrillation, and high New York Heart Association class; age was not among them.

We were surprised by the increased cost in the off-pump patients. Most of this increase occurred in the operating room. In

the off-pump patients most of the costs associated with perfusion are eliminated. However, in our experience this did not compensate for the increased costs in the off-pump patients because of the disposable equipment necessary for off-pump bypass and because off-pump operations took longer.

When we compared the off-pump and on-pump patients by propensity-matched quintiles, mortality was higher in the off-pump patients in the fifth quintile. In the fifth quintile the off-pump patients were very dissimilar from the on-pump patients, and in this quintile are located the high-risk patients who underwent off-pump surgery because the risk of on-pump surgery was believed to be too high. We believe these high-risk off-pump patients account for the increased mortality in the off-pump patients in the fifth quintile.

Access to ***The Journal of Thoracic and Cardiovascular Surgery Online*** is reserved for print subscribers!

Full-text access to ***The Journal of Thoracic and Cardiovascular Surgery Online*** is available for all print subscribers. To activate your individual online subscription, please visit ***The Journal of Thoracic and Cardiovascular Surgery Online***, point your browser to <http://www.mosby.com/jtcvs>, follow the prompts to **activate your online access**, and follow the instructions. To activate your account, you will need your subscriber account number, which you can find on your mailing label (*note*: the number of digits in your subscriber account number varies from 6 to 10). See the example below in which the subscriber account number has been circled:

Sample mailing label

This is your subscription
account number →

*****3-DIGIT 001	
SJ P1	
FEB00 J027 C: 1	(1234567-89) U 05/00 Q: 1
J. H. DOE, MD	
531 MAIN ST	
CENTER CITY, NY 10001-0001	

Personal subscriptions to ***The Journal of Thoracic and Cardiovascular Surgery Online*** are for individual use only and may not be transferred. Use of ***The Journal of Thoracic and Cardiovascular Surgery Online*** is subject to agreement to the terms and conditions as indicated online.