Should Off-Pump Coronary Artery Bypass Grafting Be Abandoned?

Harold L. Lazar, MD

One of the most controversial areas of cardiac surgery has been whether off-pump coronary artery bypass graft (OPCAB) surgery is superior to traditional on-pump coronary artery bypass graft (CABG) surgery. On-pump CABG surgery has been an effective, safe, and time-proven technique and is the gold standard with which all other surgical revascularization methods have been compared. However, performing coronary revascularization on cardiopulmonary bypass (CPB) can result in myocardial ischemic injury, neurocognitive deficits, and strokes and activate inflammatory pathways that contribute to pulmonary, renal, and hematologic complications. OPCAB offered a promising alternative strategy that had the potential to decrease perioperative morbidity, mortality, and cost by eliminating CPB. In fact, throughout Asia and particularly in India, 95% of CABG surgery is performed off-pump. In North America, OPCAB procedures peaked at 25% in 2004 and have declined steadily since that time. It is a more technically demanding procedure and results in less complete revascularization. There is growing concern that OPCAB is associated with reduced long-term graft patency and increased need for revascularization procedures and results in inferior long-term survival compared with traditional on-pump CABG surgery.

In view of these concerns, should OPCAB be abandoned? The purpose of this review is to examine clinical data that most accurately compare the advantages and disadvantages of OPCAB to determine what, if any, role it should have in the practice of surgical coronary artery revascularization. To reach these conclusions, retrospective nonrandomized, prospective randomized, and meta-analyses trials will be reviewed. The effect of incomplete revascularization and conversion to conventional CABG will be examined. The relationship between OPCAB and the inflammatory response, neurological and cognitive changes, and quality of life will be studied, and the impact of OPCAB on sex, renal transplant recipients, and elderly patients will be determined.

Retrospective Studies

Retrospective studies were largely single center and lacked randomization. Surgeons who were more skilled in OPCAB were more likely to perform these procedures. Hence, there was a significant selection bias. In most studies, the intention-to-treat principle was not honored. Therefore, if a patient was converted to an on-pump CABG, an adverse outcome associated with this patient would be attributed to the on-pump CABG and not the originally planned OPCAB. Earlier studies may have lacked proper stabilizing equipment and intracoronary perfusion devices. Many trials reported only short-term outcomes. The retrospective studies discussed in this section generally involve ≥1 surgeon, had larger sample sizes to detect statistically significant differences in clinical outcomes, and contained long-term data.

One of the largest databases used to compare outcomes between OPCAB and on-pump CABG techniques involved the New York State Registry for CABG Surgery. Racz and coworkers first compared the short- and long-term outcomes after off- and on-pump CABG surgery in New York State between 1997 and 2000. Of 68,000 CABG patients, 9,000 surgeries were performed with OPCAB techniques. There was no difference in 30-day or in-hospital risk-adjusted mortality or the incidence of perioperative myocardial infarction (MI), wound infections, renal failure requiring dialysis, or respiratory failure between the groups. OPCAB patients had a significantly higher incidence of gastrointestinal complications (1.2% versus 0.9%; P=0.003). On-pump CABG patients had a significantly higher incidence of stroke (2.0% versus 1.6%; P=0.003) and bleeding requiring reoperation (2.2% versus 1.6%; P<0.001) and had an average hospital length of stay that was 1 day longer than that of OPCAB patients. However, after 3 years of follow-up, on-pump CABG patients had a higher survival rate (89.6% versus 88.8%; P=0.022) and less need for repeat revascularization (percutaneous coronary intervention or CABG) (84.7% versus 82.1%; P<0.0001). Hannan and coworkers then reported on an additional group of patients in the New York State database (13,889 OPCAB versus 35,941 on-pump CABG) between 2001 and 2004. There was no difference in observed 30-day mortality, but risk-adjusted mortality rates favored OPCAB patients (P=0.002). In the 226 patients (1.63%) who were converted from OPCAB to on-pump CABG, the 30-day/in-hospital mortality rate was 9.73%. OPCAB patients had a significantly lower risk-adjusted rate for stroke and respiratory failure but a higher rate of unexplained surgery during the same hospital admission. In risk-matched patients, there was no difference in 3-year mortality, but OPCAB patients had higher rates of subsequent need for revascularization (89.9% versus 93.6%; 95.8% versus 93.6%; P=0.002). Two other randomized, and meta-analyses trials will be reviewed. The need for revascularization procedures and results in inferior long-term survival compared with traditional on-pump CABG surgery.

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Prospective, Randomized Trials

Prospective, randomized trials have been criticized because they lack adequate power to assess clinical outcomes, they were performed in single centers, and the surgeons involved did not perform both the on-pump and off-pump procedures. The Randomized On/Off Bypass (ROOBY) trial attempted to assess the role of OPCAB by avoiding the shortcomings of previous prospective randomized trials. This prospective, single-blinded randomized trial involved 2203 patients in 18 Veterans Affairs medical centers and 53 attending surgeons. Inclusion criteria included urgent/ elective CABG cases. Exclusion criteria included emergent/salvage CABG, CABG plus valve procedures, and patients with target vessels <1.1 mm and diffuse distal disease. The primary short-term end point was death and major adverse cardiovascular events within 30 days. Primary long-term end points (30 days to 1 year) included death from any cause, nonfatal MI, and the need for repeat revascularization. Secondary end points included completeness of revascularization, graft patency at 1 year, and neuropsychological testing. The estimated Society of Thoracic Surgeons risk scores and patient risk factors were similar in both groups. There was no difference in 30-day mortality or short-term major adverse cardiovascular events. OPCAB patients received significantly fewer grafts per patient. After 1 year, cardiac-related death (8.8% versus 5.9%; P=0.01) and major adverse events (9.9% versus 7.4%; P=0.04) were significantly higher in the OPCAB group. Furthermore, graft patency was significantly lower in the OPCAB group (82.6% versus 87.8%; P<0.001). There was no difference in neuropsychological testing between the groups. The results did not differ when the surgery was performed by a resident or attending physician or a high- or low-volume surgeon. Critics noted that women were excluded from the study, and there were no data regarding low-density lipoprotein levels, the use of statins and aspirin, or whether glycemic control was practiced in these patients. They also point to the fact that the conversion rate to on-pump CABG was 12.4%, which is significantly higher than the 2.2% found in the Society of Thoracic Surgeons database and suggests that this reflects the inexperience of the ROOBY OPCAB surgeons. On the contrary, the high conversion rate was attributable to the fact that because of the randomization process, the ROOBY surgeons had to attempt to perform the OPCAB and could not be selective, as was the case in other trials. Short-term prospective trials were in agreement with the ROOBY trial in that there was no difference in morbidity and mortality after 30 days between the OPCAB and on-pump CABG groups. Khan and coworkers showed that 3 months after surgery, there was a significant decrease in overall graft patency (88% versus 98%; P=0.002) in patients undergoing OPCAB. Michaux and coworkers found that right ventricular function was preserved in both OPCAB and on-pump CABG patients 3 months after surgery. In a study involving high-risk patients with 3-vessel disease and a EuroSCORE ≥5, Møller and coworkers could find no difference in morbidity or mortality between the 2 groups.

The Surgical Management of Arterial Revascularization Therapy (SMART) trial examined long-term survival and graft patency in a prospective, randomized trial involving 297 patients after isolated elective CABG. It was a single-center, single-surgeon trial among survivors who volunteered to return for clinical evaluation and imaging studies. Of the 140 survivors, only 87 were willing to have the full detailed follow-up and imaging studies. This represented only 44% of the original sample and 62% of the surviving patients. After 7.5 years of follow-up, there was no difference in mortality or late graft patency between OPCAB and on-pump CABG. Although recurrent angina was more common in the OPCAB group, this did not reach statistical significance. Hence, this study, performed by one of the world’s experts in OPCAB surgery, could not demonstrate any superiority of OPCAB over on-pump CABG.

Recently, Lamy and coworkers reported on the 1-year outcomes of the Coronary Artery Bypass Surgery Off or On...
Pump Revascularization Study (CORONARY). This prospective study involved 4752 patients randomized to either on- or off-pump CABG in 79 centers and 19 countries. The 1-year outcomes included (1) a composite rate of death, nonfatal cerebrovascular accident, nonfatal MI, or new nonfatal renal failure requiring dialysis and (2) the same composite outcome plus the need for repeat coronary revascularization. In addition, a European Quality of Life–5 Dimensions Questionnaire and the associated visual-analog scale were used to assess quality of life, and neurocognitive function was assessed with the use of 3 neurocognitive tests: the Montreal Cognitive Assessment, the Digit Symbol Substitution Test, and the Trail Making Test Part B.

After 1 year, there was no difference in the primary outcome event rate between groups (12.1% off-pump versus 13.3% on-pump; \( P=0.24 \)). The incidence of the individual components of the primary outcome also did not differ. There were also no significant differences between the groups in the incidence of recurrent angina (1.0% off-pump versus 0.9% on-pump), but the need for repeat revascularization was higher in the off-pump group and approached statistical significance (1.4% off-pump versus 0.8% on-pump; \( P=0.07 \)). Furthermore, there was no significant difference between the 2 groups in the quality of life scores. Although there was a small difference in cognitive function in favor of the off-pump group at discharge, this did not persist after 1 year. Hence, there were no significant differences between the 2 groups at 1 year in the measures of quality of life or neurocognitive function.

Compared with the ROOBY trial, the CORONARY trial included twice as many participants. Each off-pump procedure was performed by an experienced surgeon who had >2 years of experience and had performed >100 OPCAB cases. Trainees were not allowed to be the primary surgeon. The rate of crossover from the off-pump to the on-pump group was lower in the CORONARY trial (7.9% versus 12.4%), suggesting a higher level of surgical expertise. Nevertheless, despite the improved technical experience of highly qualified off-pump surgeons, the need for revascularization remained higher in the off-pump group.

**Meta-Analyses**

Numerous meta-analyses have reviewed the short- and long-term outcomes of OPCAB versus on-pump CABG.\(^{17-27}\) The findings of these studies are summarized in the following paragraphs.

There was no difference in short-term morbidity or mortality between the 2 procedures.\(^{17,19,20,24-26}\) Reston and coworkers\(^{18}\) and Afifalo and coworkers\(^{28}\) found a significantly lower incidence of early strokes in the OPCAB group, but no mention is made of the incidence of calcified ascending aortas or the cross-clamp techniques used in these studies. Patients undergoing OPCAB surgery tended to have a significant decrease in the number of grafts and a higher incidence of incomplete revascularization.\(^{19,21-23}\) OPCAB was associated with decreased graft patency and a higher incidence for the need for repeat revascularization.\(^{17-19,22,25-27}\) Several studies that initially showed favorable early outcomes with OPCAB found that these beneficial effects were no longer apparent in the long term. Reston and coworkers\(^{18}\) found in 46621 patients that OPCAB resulted in a significantly lower incidence of MI, cerebrovascular accident, reoperation for bleeding, renal failure, atrial fibrillation, and wound infections within 30 days of surgery. However, long-term follow-up showed that the need for repeat interventions (percutaneous coronary intervention or CABG) and the incidence of death were significantly lower in the on-pump CABG group. Jarral and coworkers\(^{21}\) in 7759 patients found that the 30-day mortality in OPCAB patients with left ventricular dysfunction was significantly reduced. However, this beneficial effect was no longer apparent in the long term because there was no difference in morbidity between OPCAB and on-pump CABG patients. The authors hypothesize that the significant increase in incomplete revascularization in the OPCAB patients may have contributed to the decrease in long-term survival. The same findings were noted by Takagi and coworkers,\(^{22}\) who found that OPCAB increased late mortality by a factor of 1.37 (\( P=0.024 \)) over on-pump CABG over a 6-year follow-up. The OPCAB group had a significantly higher incidence of incomplete revascularization and decreased graft patency. A higher long-term need for repeat revascularization was also noted by Wijesundera and coworkers\(^{26}\) in their meta-analysis of 37 randomized, controlled trials. The economic impact of OPCAB versus on-pump CABG was analyzed by Chu and coworkers\(^{24}\) using a meta-analysis involving 63 000 patients from a Nationwide Inpatient Database. Although there was no difference in hospital mortality between the groups, OPCAB patients had significantly longer hospital stays and higher hospital costs. Multivariate analyses showed that OPCAB independently accounted for an additional 0.6 day of hospital stay (\( P<0.0001 \)) and $1497 more in hospital costs per patient (\( P<0.01 \)).

**OPCAB and Incomplete Revascularization**

The data from these meta-analyses suggest that the decreased benefits from OPCAB in the long term may be attributable to the higher incidence of incomplete revascularization associated with this technique. Despite advances in stabilizers and other equipment, it may be difficult to graft inferior and posterolateral vessels because of right ventricular and left ventricular distension and hemodynamic changes. Synnergren and coworkers\(^{28}\) examined the effect of incomplete revascularization over a 5-year period in a nonrandomized cohort of 9408 patients. Leaving 1 diseased vascular segment without a bypass graft resulted in no increased risk of death. However, leaving 2 vascular segments unvascularized significantly increased the risk for mortality (\( P=0.01 \)). Furthermore, incomplete revascularization was more common in the off-pump group (\( P<0.001 \)). In patients with 3-vessel disease, survival was significantly less (\( P<0.001 \)) after OPCAB procedures. Similar findings were noted by Caputo et al\(^{29}\) in a cohort of OPCAB patients. Incomplete revascularization is especially detrimental in older patients (>75 years) and results in a significant decrease in long-term survival.\(^{30,31}\)

**Patients Who Require Conversion From OPCAB to On-Pump CABG**

In most analyses of OPCAB patients, data have not been analyzed with the intention-to-treat principle. Hence, a
Does OPCAB Limit the Detrimental Effects Associated With CPB?

A major impetus for performing OPCAB was to avoid the detrimental effects of CPB, which include activation of inflammatory pathways, changes in neurological and cognitive function, and alterations in quality of life. However, patients undergoing OPCAB have not shown any benefits in these areas.

Inflammatory Responses and Biomarkers

It has been postulated that avoiding CPB with OPCAB would decrease the severity of the systemic inflammatory response seen with on-pump CABG patients that contributes to organ failure and increased morbidity and mortality. However, several clinical studies have found that there is significant activation of the inflammatory response in both on- and off-pump patients that is not explained by the type of revascularization strategy that is used. Although some investigators have shown that OPCAB may decrease complement activation, there is no difference in the production of cytokines or chemokines that modulate neutrophil and platelet activation. Caution should be exercised in interpreting data involving on-pump CABG and OPCAB and the activation of inflammatory pathways. In some studies, only a limited number of mediators were measured, which does not necessarily reflect the entire systemic inflammatory response. Castellheim and coworkers studied 25 biomarkers, of which 14 increased in both on-pump CABG and OPCAB patients; only 3 showed significant differences between groups. They concluded that delayed stroke remains a problem after both OPCAB and on-pump CABG. This study has the same limitations noted in other series. It is retrospective and lacks information regarding the quality of the aorta and the clamping techniques used. With the use of the single-clamp technique, the incidence of strokes after on-pump CABG has declined significantly. Furthermore, OPCAB does not completely eliminate the need for aortic clamping, and there is still the potential for neurological injury during periods of hypotension and during manipulation of the ventricle.

Studies have failed to show that OPCAB prevents the decline in cognitive function seen after coronary revascularization. In general, patients with coronary artery disease have a higher prevalence of cerebrovascular disease. Van Dijk and coworkers reported the results of neurocognitive outcomes over 5 years after OPCAB and on-pump CABG in a randomized, multicentered trial involving 281 patients. There was no difference in either cognitive outcomes or cardiovascular events between the groups. In this trial, half of all patients undergoing any coronary procedure had evidence of cognitive dysfunction compared with baseline. Hence, advanced age and atherosclerosis may be more important determinants of long-term cognitive dysfunction than the type of CABG procedure performed. Recently, Kennedy and coworkers reported their findings on cognitive outcome after on- and off-pump CABG in a meta-analysis of 13 randomized, controlled trials involving 2405 patients using 7 psychometric tests. No significant differences were found between on- and off-pump patients in any of the tests after 1 year.

Quality of Life

OPCAB has also failed to demonstrate improvements in quality of life over on-pump CABG. The Beating Heart Against Cardioplegic Arrest Study (BHACAS) 1 and 2, a randomized, controlled trial of on- versus off-pump surgery, was the subject of a study by Fu and coworkers involving 5359 patients with a mean
follow-up of 5 years. Overall 30-day mortality was significantly higher in women for all revascularization techniques. Female sex was an independent risk factor after on-pump CABG but not OPCAB, for which there was no significant difference between male and female patients. However, there was no difference in late survival between either male or female patients regardless of whether they received OPCAB or on-pump CABG. Female patients undergoing OPCAB were significantly less likely to have received complete revascularization as judged by the number of vessels bypassed versus the number of vessels diseased. They were also less likely to be free from long-term major cardiac and cerebral events compared with women treated with on-pump CABG. Fu and coworkers postulated that these inferior late results could be explained in part by the higher incidence of incomplete revascularization in the OPCAB women. Puskas and coworkers also found that OPCAB was associated with a significant reduction in early mortality in women. However, in a follow-up study in this same group, OPCAB and on-pump CABG resulted in similar survival regardless of sex after 10 years. The end point of this study was all-cause mortality and did not include nonfatal events such as stroke or the need for repeat revascularization.

Supporters of OPCAB have claimed that this technique limits renal dysfunction, especially in high-risk patients. To further test this hypothesis, Shayan and coworkers retrospectively studied 43 renal transplant recipients who required coronary revascularization and had functioning allografts after renal transplants. In this cohort, 21 patients received OPCAB, and 22 had on-pump CABG. OPCAB patients were significantly older, whereas on-pump CABG patients had a significantly higher incidence of reoperative surgery. The on-pump CABG group received significantly more bypass grafts, but there was no difference in 30-day or 8-year survival between the groups. Immediate peak creatinine levels were significantly higher in the on-pump CABG group, but there was no difference in 30-day or 8-year survival groups. The authors concluded that despite the avoidance of CPB, OPCAB resulted in no improvement in patient survival. The secondary end points included operating room time, duration of mechanical ventilation, transfusion requirements, and intensive care unit and hospital length of stay.

There was no difference in the primary composite end point (7.0% off-pump versus 8.0% on-pump; P=0.40). However, additional revascularization procedures within 30 days were more frequent in the off-pump group (1.3% versus 0.3%; P=0.03). Patients in the off-pump group were less likely to receive blood products; however, the study had no protocols to determine when transfusions should be given. There was no difference in any of the other secondary end points. The mean number of grafts was significantly less in the off-pump group (2.7% versus 2.8%; P<0.001). The authors concluded that off-pump CABG did not improve outcomes in these elderly high-risk patients. Furthermore, concerns were raised that the increased need for early revascularization and the decreased number of grafts in the off-pump group would lead to an increased incidence of future cardiovascular events, thus exposing these elderly patients to increased morbidity and mortality.

Potential Areas for OPCAB Revascularization
OPCAB may play a role in 2 clinical scenarios. Patients with a porcelain or atherosclerotic aorta in whom there is increased risk for aortic trauma or cerebral embolization may be best revascularized with the use of OPCAB techniques. However, these procedures can also be performed while the patient is on CPB in a vented heart with the use of stabilizer equipment. Patients with liver failure or cirrhosis, in whom periods of prolonged heparinization should be avoided, may also benefit from OPCAB techniques.

Conclusions
Should OPCAB be abandoned for coronary artery revascularization?
Retrospective nonrandomized, prospective randomized, and meta-analyses trials have failed to show any significant improvement in short-term morbidity or mortality with OPCAB techniques. Even in those studies in which OPCAB has resulted in a small improvement in early postoperative outcomes, these improvements are no longer apparent on long-term follow-up. In fact, several studies suggest that long-term survival may be significantly reduced in OPCAB patients compared with patients in whom on-pump techniques were used. This may be attributable to the significant increase in incomplete revascularization seen in OPCAB patients and may be responsible for the increase in recurrent angina and need for revascularization procedures seen in OPCAB.
patients. Proponents of OPCAB may argue that fewer grafts are performed during OPCAB procedures because surgeons are more likely to perform OPCAB on patients with single- and double-vessel disease. However, studies defining complete revascularization as the ratio of grafted versus diseased vessels continue to show that OPCAB patients are underrevascularized, regardless of the surgical anatomy. Furthermore, studies in which graft patency has been assessed show that OPCAB patients have a significant decrease in overall long-term graft patency.

Proponents of OPCAB have suggested that data derived from early trials underestimate the true value of this approach. They argue that with the appropriate use of modern stabilizers, heart positioning devices, intracoronary shunts, and adequate surgeon experience, similar completeness of revascularization and graft patency can be achieved. However, single cross-clamp techniques and the use of heparin-bonded and miniaturized pump circuitry have reduced the detrimental effects of CPB seen previously in on-pump CABG patients during this same time period. Furthermore, 2 recent trials in which OPCAB was performed by experienced off-pump surgeons have failed to show any superiority of this technique over on-pump CABG and continue to show a higher incidence of repeat revascularization in off-pump patients.16,64

Some have argued that OPCAB be only performed in high-volume centers by surgeons who have developed a high level of expertise with this technique. It has been recommended that the learning curve for OPCAB is between 50 and 75 cases.65 However, with the volume of CABG surgery continuing to decline worldwide, this number will take longer to reach, especially as the complexity of coronary lesions increases, ejection fractions decrease, and comorbidities of patients increase. It will be particularly difficult for younger surgeons to attempt to master this more difficult technique despite reduced patient volume.

As CABG volume continues to decline, some surgeons have used OPCAB to compete for more market share. Hospitals and individual and group physicians have marketed themselves to the public through advertising and the Internet, promising less morbidity and mortality and a faster return to work with less cognitive dysfunction and a better quality of life with OPCAB. This has prompted patients and referring physicians to insist that OPCAB be performed even in cases of poor distal targets, hemodynamic instability, and marked cardiomegaly when it is not in the best interest of the patient to do so.

OPCAB has made surgeons lose their focus in regard to the goals of surgical coronary revascularization. Surgeons should strive to perform the most complete revascularization, a technically perfect anastomosis, using the best conduits with the minimal amount of hemodynamic instability. The procedure should be able to be performed under all circumstances, on all patients, at all institutions, regardless of their cardiac volume. Emphasis should be placed on perioperative glycemic control and enhancement of graft patency with the use of statins, aspirin and other antiplatelet agents, and angiotensin-converting enzyme inhibitor therapy when appropriate. We must not forget that patients are sent for surgical revascularization because medical management has failed, their cardiologists believe that stents will not result in complete revascularization, and the goal is for optimal long-term survival and enhanced freedom from recurrent angina and the need for rerevascularization. These goals can be best achieved with on-pump CABG surgery. The data, derived from numerous studies worldwide, clearly demonstrate that OPCAB has failed to meet these goals. Unless individual surgeons can demonstrate that they can achieve short- and long-term outcomes with OPCAB that are comparable to on-pump CABG results, they should abandon this technique.

Disclosures

None.

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