The gold standard for multivessel coronary revascularization continues to be coronary artery bypass grafting (CABG). Despite advances in percutaneous coronary intervention (PCI) and medical therapy, CABG still plays a major role in the treatment of patients with coronary disease. Although an abundance of literature comparing on-pump (ONCAB) vs. off-pump (OPCAB) CABG exists, the optimal surgical strategy remains in question. The interest in off-pump techniques has largely been driven by the increased awareness of the deleterious effects of cardiopulmonary bypass (CPB) and aortic manipulation. Although many surgeons and centers have reached a plateau in recent years and currently accounts for only approximately one-fifth of revascularizations performed, with the majority of CABG being performed on-pump worldwide. Advocates of the ONCAB approach cite low morbidity and mortality, with outcomes that have continued to improve despite a surgical patient population with increasing comorbid medical conditions and more severe coronary disease. However, complications such as renal failure and stroke continue to occur. These complications may occur not only because of the systemic inflammatory activation that occurs with extracorporeal circulation, but also because of the manipulation of the aorta required for cannulation, CPB, and aortic clamping. For most surgeons, the lack of compelling evidence in randomized controlled trials supporting OPCAB over ONCAB has been an impediment to implementing this strategy in routine practice. Furthermore, many surgeons consider an off-pump approach more technically challenging and demanding. Other points of controversy include mixed reports on graft patency, completeness of revascularization, and the need for repeat revascularization. Recent studies have suggested that certain high-risk patient subgroups are more likely to benefit from an OPCAB approach. These include patients with advanced ascending aortic atherosclerosis, ventricular dysfunction, renal insufficiency, diabetes, advanced age, and chronic lung disease, all of which tend to be increasingly common among patients referred for CABG. In these high-risk patients, avoiding the deleterious effects of CPB and minimizing or avoiding aortic manipulation may lead to improved short-term outcomes. Therefore, it is important for coronary surgeons to be facile with OPCAB techniques in order to implement this strategy when warranted.

**Key Words:** Cardiopulmonary bypass; Coronary revascularization; Off-pump bypass surgery

Since the refinement of OPCAB techniques, several randomized trials have reported significant advantages of OPCAB over ONCAB with respect to transfusion requirement, myocardial enzyme release, duration of mechanical ventilation, ICU and hospital lengths of stay, and cost-effectiveness. However, those trials have not shown an in-hospital mortality advantage for OPCAB compared with ONCAB, perhaps because of the small sample sizes and enrollment of predominantly low-risk patients. In a meta-analysis of 37 randomized controlled trials supporting OPCAB over ONCAB, the lack of compelling evidence in randomized controlled trials has been an impediment to implementing this strategy in routine practice. Therefore, it is important for coronary surgeons to be facile with OPCAB techniques in order to implement this strategy when warranted.
trials (3,369 predominantly low-risk patients), no significant differences were found for 30-day mortality between OPCAB and ONCAB (odds ratio (OR), 1.02; 95% confidence interval (CI) 0.58–1.80). In the largest multicenter randomized trial to date comparing OPCAB with ONCAB (2,203 patients), Shroyer et al did not demonstrate a difference in 30-day composite outcome of death or complications. Only 1 randomized prospective study has demonstrated a reduction in hospital mortality with OPCAB compared with ONCAB, and this was in patients who underwent emergency surgery for ST-segment elevation myocardial infarction with cardiogenic shock within 6 h of the onset of symptoms. However, in retrospective, observational analyses a mortality benefit has been demonstrated for OPCAB. In a study by Hannan et al, 49,830 patients from the New York State registry underwent risk-adjusted analysis (Cox proportional hazard models and propensity analysis) comparing outcomes after OPCAB vs. ONCAB. In that study, OPCAB patients had significantly lower 30-day mortality (adjusted OR 0.81, 95%CI 0.68–0.97, P=0.0022). In a large registry study from California assessing CABG outcomes, Li et al also demonstrated a significant reduction in propensity-adjusted operative mortality with OPCAB compared against ONCAB (2.59%, 95%CI 2.52–2.67% vs. 3.22%, 95%CI 3.17–3.27%). One advantage of registries is that they represent an analysis that is representative of a typical patient population spectrum, free of the selection biases involved in randomized trials. A limitation of randomized trials is the relatively low sample size, which can increase the probability of Type I error, especially when trying to detect differences for an infrequent event, such as mortality. Large-scale reviews are adequately powered to detect significant differences in adverse outcomes across a broad patient population, and should not be minimized when compared with randomized trials. An intention-to-treat retrospective analysis of 42,477 patients from the Society of Thoracic Surgeons (STS) National Database showed a reduction in risk-adjusted operative mortality (adjusted OR 0.83, P=0.03) in addition to numerous morbidity outcomes favoring patients undergoing OPCAB. Challenging the previously mentioned registry and STS database conclusions, another large retrospective review failed to demonstrate a mortality advantage for OPCAB. Assessing 63,000 patients in the Nationwide Inpatient Sample administrative (rather than clinical) database, Chu et al found no difference in hospital mortality between OPCAB and ONCAB (3.0% vs. 3.2%, P=0.14). Palmer et al and Williams et al have similarly reported that hospital mortality was equivalent, although those studies were substantially smaller with fewer than 6,000 patients.

A significant issue with OPCAB that has a significant potential to adversely affect outcomes is the occasional requirement of emergency conversion to cardiopulmonary support. Precipitating factors are usually profound and acute hemodynamic compromise, because of poorly tolerated regional ischemia, increased valvular regurgitation from cardiac positioning, bradycardia during right-sided or inferior wall grafting, or intractable ventricular tachycardia/fibrillation. It has become well-recognized that an emergency conversion (“crash on pump”) to ONCAB is associated with significantly higher perioperative morbidity and mortality. Mortality specifically for converted patients has ranged from 6% to 15%. Early skeptics of OPCAB appropriately criticized observational comparisons of outcomes after OPCAB vs. ONCAB because such studies were not analyzed on an intention-to-treat basis. Most publications now include patients who were converted urgently or emergently to on-pump in the OPCAB group. In more recent studies, Patel et al reported a significantly increased in-hospital mortality rate of 12% in those converted urgently to ONCAB compared with 1.5% in those who did not require urgent conversion. Similarly, Jin et al reported results from a large registry of over 70,000 patients in which 5.8% of cases that began off-pump were converted to on-pump. In this group, hospital mortality was significantly higher in converted patients compared with OPCAB patients or patients initially performed on-pump (9.9% vs. 1.6% vs. 3.0%, respectively). Importantly, there does not appear to be an increased risk of complications in patients who are electively converted to ONCAB. This situation usually occurs when the surgeon or anesthesiologist becomes aware of hemodynamic instability during a test period of regional ischemia or during initial cardiac positioning, displacement, or stabilization. In such circumstances, once the maneuvers are reversed, the hemodynamic status tends to improve, and the decision can then be made to proceed with an on-pump approach under a more controlled scenario.

Mid- and Long-Term Mortality

Several studies have demonstrated comparable mid-term and long-term survival among OPCAB and ONCAB patients. With sensitivity analysis, 1-year mortality from cardiac causes was slightly higher in the OPCAB group compared with the ONCAB group (2.7% vs. 1.3%, P=0.03). Therefore, the 1-year results from this multi-institutional randomized trial need to be compared with the previously mentioned randomized and observational analyses that have longer follow-up and which have consistently shown comparable mid- and long-term mortality rates. Moller et al recently published mid-term outcomes from their randomized trial (The Best Bypass Surgery Trial) comparing OPCAB vs. ONCAB. With a median follow-up of 3.7 years, all-cause mortality was significantly increased in the OPCAB group (24% vs. 15%; HR 1.66, 95%CI 1.02–2.73; P=0.04), but cardiac-related death was not significantly different (10% vs. 7%; HR 1.30, 95%CI 0.64–2.66; P=0.47). After 5-year follow-up from the MASS III randomized trial, Hueb et al reported no difference between OPCAB and ONCAB for a primary composite endpoint that included death, myocardial infarction, further revascularization (surgery or angioplasty), or stroke. Furthermore, Puskas et al, in a randomized trial of 200 patients with mean follow-up of 7.5 years, demonstrated that OPCAB and ONCAB were associated with similar early and late graft patency rates, incidence of recurrent or residual myocardial ischemia, need for reintervention, and long-term survival.
July through December 2000, and also ascertained each patient’s vital status through 2007 using the National Death Index. The 7-year Kaplan-Meier survival rates were 71.2% and 73.4% (P=0.07) for OPCAB and ONCAB surgery, respectively, and there was no difference in baseline risk factors.

High-Risk Patients

It is intuitive to believe that OPCAB may be particularly beneficial in patients with known risk factors for adverse events with CPB and aortic clamping, cannulation or manipulation. The perceived benefits of OPCAB may become more apparent in high-risk patients, especially those with chronic obstructive pulmonary disease, renal insufficiency, and advanced atheromatous disease of the ascending aorta. Several studies have assessed this difference. In a randomized prospective study by Møller et al., 341 high-risk patients (EuroSCORE ≥5) were enrolled to either multivessel OPCAB or ONCAB. The initial 30-day composite outcome of major adverse cardiac and cerebrovascular events was similar between groups (15% vs. 18%, risk ratio (RR) 0.83, 95%CI 0.52–1.34). However, there was a trend toward reduced all-cause 30-day mortality in the OPCAB group (3.4% vs. 6.7%, RR 0.51, 95%CI 0.19–1.34). A lack of statistical difference may have been related to the small sample size. Recently, Emmert et al reported an evidence in an interim analysis of 411 high-risk patients in a multicenter, prospective, randomized trial the composite primary endpoint (operative mortality, myocardial infarction, stroke, renal failure, reoperation for bleeding and adult respiratory distress syndrome) was significantly lower in the OPCAB group (5.8% vs. 13.3%, P=0.010). 37

Several retrospective studies have documented improved outcomes in higher-risk patients undergoing OPCAB. Dewey et al showed improved operative mortality after OPCAB among patients with dialysis-dependent renal failure. 38 However, Shroff et al reported only a modestly increased survival advantage for OPCAB patients on dialysis, and the benefit was most marked early after OPCAB. 39 More favorable outcomes have been reported with OPCAB compared with ONCAB in patients with left ventricular dysfunction, previous sternotomy, advanced age, previous stroke, and female sex. 40–47 Emmert et al reported excellent outcomes in patients with left main (LM) disease undergoing OPCAB. 48 Furthermore, Murri et al demonstrated in a propensity analysis that OPCAB in patients with LM stem disease is a safe procedure with reduced early morbidity and mortality and similar long-term survival compared with conventional ONCAB. 49 Emmert et al showed a lower mortality rate (1.1% vs. 3.8%; P=0.018) and superior postoperative outcomes in diabetic patients with multivessel disease undergoing OPCAB vs. ONCAB. 50 Takase et al 51 and Vasques et al 52 have shown that OPCAB can be performed safely in octogenarians, with excellent early and late outcomes. Kuss and Borgermann, in an ecologic regression analysis of 86 randomized trials with total population of 9,906 patients, found superior mortality and atrial fibrillation outcomes after OPCAB compared with ONCAB in patients with left ventricular dysfunction. 43 In a large retrospective cohort (14,766 patients), Puskas et al reported that patients in the highest risk quartile had a significant reduction in hospital mortality with OPCAB compared with ONCAB (3.2% vs. 6.7%, P<0.0001, OR 0.45 95%CI 0.33–0.63, P<0.0001). 54 There was no significant difference in operative mortality between OPCAB and ONCAB for patients in the lower 3 risk quartiles. Thus, patients with an STS predicted risk of mortality >2.5% had a survival advantage with OPCAB. That study provides further support that OPCAB may disproportionately benefit high-risk patients.

Neurological Outcomes

There have been no randomized prospective trials that have shown a reduction in stroke with OPCAB compared with ONCAB. Numerous large retrospective analyses have shown that OPCAB may be associated with a reduced incidence of stroke compared with ONCAB. 17,31,46,49,50,55,56 Mishra et al performed a propensity matched comparison of OPCAB vs. ONCAB in 6,991 patients with atheromatous aortic disease and found a significant decrease in postoperative stroke (0.50% vs. 0.97%; P=0.05), with OPCAB being the only independent predictor of a decreased stroke rate in the multivariate analysis. 57 Hamann et al reported a highly significant risk-adjusted decrease in perioperative stroke with OPCAB vs. ONCAB (adjusted OR 0.70, 95%CI 0.57–0.86, P=0.0006). 58 Nishiyama et al reported that OPCAB was associated with a significant reduction in early stroke compared with ONCAB (0.1% vs. 1.1%, P=0.0009). 59 The temporal patterns of stroke reduction in this study suggest that the majority of early strokes are from aortic emboli and that operative factors such as aortic manipulation during surgery are likely responsible for early postoperative stroke. In contrast, postoperative stroke was not significantly reduced in 2 recent meta-analyses of OPCAB vs. ONCAB among relatively low-risk patients. 60,61 Furthermore, in 2 other studies, Williams et al 62 and Chu et al 63 did not find any differences in stroke between OPCAB and ONCAB.

Recently in a meta-regression analysis of 59 randomized trials encompassing 8,961 patients, Afilalo et al showed a significant 30% reduction in the occurrence of postoperative stroke with OPCAB (RR 0.70, 95%CI 0.49–0.99). 64 Yet, the mechanisms responsible for the observed reduction in postoperative stroke have not been well-defined in most of these studies. Although eliminating the need for aortic cannulation, CPB, and application of a cross-clamp, OPCAB does not consistently eliminate the need for construction of aortocoronary proximal anastomoses. Furthermore, partial aortic clamping for construction of proximal anastomoses is still routinely performed in most patients undergoing OPCAB. Thus, the benefits of OPCAB may be offset because of aortic manipulation and the atheroembolic-associated risk with partial aortic clamping. There is evidence in the literature that avoidance of such manipulation and clamping may reduce neurological adverse effects. Kim et al reported a lower incidence of postoperative stroke in patients undergoing OPCAB without any manipulation of the aorta as opposed to patients undergoing OPCAB with partial clamping and patients undergoing ONCAB. 65 And Scarborough et al showed that the use of OPCAB in combination with a clampless proximal anastomotic device decreased the number of intraoperative embolic events observed with transthoracic Doppler monitoring in comparison with ONCAB with hand-sewn proximal anastomoses. 66

We believe that a major indication for an OPCAB approach is the presence of advanced ascending aortic atherosclerosis as determined by intraoperative epiaortic ultrasonography (Grade III–V). Patients with a heavily diseased ascending aorta have a higher risk for embolic complications arising from dislodged atheromatous debris after cannulation, CPB, and aortic clamping. Of course, reaping the full benefit of OPCAB in such patients mandates a no-aortic-touch technique. Studies that have used transthoracic Doppler ultrasonography have confirmed the production of aortic emboli associated with cannulation and application of aortic clamps. 64,65,66 Embolic events have been shown to be decreased when aortic cannulation,
CPB, and aortic clamping are avoided, as well as with the use of clampless anastomotic devices. Therefore, it is intuitive that using such strategies to minimize aortic manipulation with off-pump techniques is the best surgical strategy in these patients. Ultimately, the effect of these different strategies on reducing postoperative stroke needs to be further investigated in prospective, large-scale trials.

Completeness of Revascularization

A major criticism among proponents of ONCAB is the ability to completely revascularize patients with multivessel coronary disease with OPCAB techniques. However, most of the evidence from randomized trials suggests equivalent completeness of revascularization between OPCAB and ONCAB. The concerns stem from the ability to perform multiple lateral wall grafts. Shroyer et al found that there fewer grafts performed than originally planned occurred more often in the OPCAB group (17.8% vs. 11.1%, P<0.001). In a meta-analysis and consensus statement of randomized trials, Puskas et al consistently demonstrated a lower number of grafts per patient in OPCAB vs. ONCAB (2.6 vs. 2.8, P<0.0001). Even analysis of later trials in which surgeon’s experience was greater still showed slightly fewer grafts performed with OPCAB vs. ONCAB (2.7 vs. 2.9 grafts).

However, completeness of revascularization and the number of grafts revascularized should not be used synonymously. A common formula has been to divide the number of grafts performed by the number of grafts needed (number of graft-able vessels with angiographically significant stenoses) by the number of grafts revascularized should not be used synonymously.

Graft Patency and Repeat Revascularization

Graft patency has been studied in 5 randomized trials from in-hospital to 1-year postoperatively, largely showing no difference in graft patency rates between OPCAB and ONCAB. Puskas et al demonstrated no difference in graft patency at discharge and at 1-year. This is in contrast to others showing a reduced graft patency with OPCAB. Shroyer et al found that the overall rate of graft patency (driven by vein graft patency) was lower in the OPCAB group compared with the ONCAB group (82.6% vs. 87.8%, P<0.001) and 3 other studies showed no difference in graft patency at 1-year.

The largest observational study to evaluate graft patency between OPCAB and ONCAB is the New York registry data from Hannan et al. Even though OPCAB was associated with lower in-hospital mortality and morbidity and equivalent long-term outcomes compared with ONCAB, the need for repeat revascularization was greater in the OPCAB group (93.6% vs. 89.9%, P<0.0001). The retrospective nature of this analysis limited the ability to differentiate whether this difference was related to incomplete revascularization during OPCAB, reduced graft patency, or to unrecognized confounding variables. Furthermore, it can be debated whether the statistical differences translate into significant clinical differences (absolute difference of 3.7%). In a recent prospective observational analysis, Hu et al showed a statistically significant increase in long-term major cardiovascular events with OPCAB compared with ONCAB (43.8% vs. 41.2%, P=0.002), although the absolute difference was small. Long-term repeat revascularization (9.4% vs. 7.6%, P=0.03), recurrent angina (39.0% vs. 26.9%, P<0.001), and cardiovascular disease-related hospitalization (56.5% vs. 41.6%, P<0.0001) were all significantly higher with OPCAB compared with ONCAB.

It is our belief that technical precision and anastomotic quality should not be compromised when deciding to proceed with OPCAB. OPCAB is associated with a learning curve, especially when grafting lateral wall targets. Therefore, patient selection is paramount and surgeons should be experienced and facile with anterior and inferior wall grafting before proceeding to the lateral wall territory. We advocate an on-pump approach if there is any question about the integrity of performing off-pump distal anastomoses, as in patients with small distal disease, intramyocardial vessels, and high lateral wall targets. With experience, however, we believe OPCAB techniques can be safely and effectively used in most cases. Other factors that may contribute to graft patency, such as platelet activation and hypercoagulability, which may be increased with OPCAB, should be taken into consideration. We routinely administer 2,000–5,000 IU of heparin prior to skin incision and vein harvesting, in addition to routinely administering dual antiplatelet therapy early in the postoperative period.

Surgical Volume and Outcomes

A major criticism of both randomized controlled trials and observational analyses is that these studies are conducted at single centers with extensive off-pump experience. Thus, critics often suggest that routine ONCAB should be used by surgeons with less expertise and that OPCAB should be performed in high-volume off-pump centers that report excellent outcomes. Konety et al recently assessed the effect of surgical volume on outcomes after OPCAB. For hospitals in the highest percent OPCAB volume quartile, adjusted mortality and complication rates were significantly lower compared with ONCAB (OR 0.50, 95% CI 0.41–0.61, P<0.001). However, in the lowest percent OPCAB volume quartile, outcomes between OPCAB and ONCAB were similar. These findings were attributed by the authors to differences in hospital organizational structures, in addition to the surgeon’s skill. This includes skilled first and second assistants, surgical technicians, operating room nurses, and anesthesia personnel, all of whom are crucial to a successful OPCAB procedure. Yet even in low volume centers, outcomes were comparable with those for ONCAB. Thus, better outcomes may be achieved with OPCAB compared with ONCAB as experience with this technique increases.
Minimally-Invasive and Hybrid Approaches

Increasing familiarity with off-pump techniques has facilitated the development and application of minimally-invasive revascularization procedures. Endoscopic atrumatic coronary artery bypass (EndoACAB) has been well described, involving a thoracoscopic or robotic-assisted left internal mammary artery dissection and harvest, followed by a direct off-pump anastomosis to the left anterior descending (LAD) coronary artery via a left anterior mini-thoracotomy.\(^{80}\) Totally endoscopic coronary artery bypass, which is facilitated by off-pump and robotic techniques with anastomotic facilitating devices, has also been well described.\(^{81}\) Hybrid coronary revascularization (HCR) is an alternative strategy that combines a minimally-invasive, sternal-sparing EndoACAB with PCI to LAD or non-LAD coronary lesions. Either staged or simultaneous, a best-matched strategy for a specific anatomic lesion is believed to be the advantage of the hybrid approach. The feasibility of the simultaneous hybrid approach has been demonstrated, with high 6-month angiographic vessel patency and minimal adverse cardiac events, similar to OPCAB groups.\(^{82,83}\)

In addition, the hybrid approach offers the benefit of shorter length of stay, lower intubation times, less pain, and less blood loss, with decreased transfusions compared with standard OPCAB. Halkos et al\(^{84}\) studied 27 patients with LM coronary disease who underwent HCR, matched 3:1 with 81 contemporaneous patients treated with the OPCAB technique. There were no perioperative deaths, strokes, or myocardial infarctions among the HCR patients, and the major adverse cardiac and cerebrovascular events were similar between groups. The incidence of blood transfusion was higher with OPCAB (50 of 81, 61.7% vs. 9 of 27, 33.3%; P=0.01). With a median of 3.2 years of follow-up, HCR patients tended to have a higher incidence of repeat revascularization compared with OPCAB (2 of 27, 7.4% vs. 1 of 81, 1.2%; P=0.09), but this was not statistically significant. Further comparison by Halkos et al\(^{85}\) assessed 147 patients with multivessel coronary disease who underwent HCR, compared with 588 patients treated with multivessel OPCAB. Major adverse events were similar between the 2 groups. With a median of 3.2 years of follow-up, the need for repeated revascularization was higher for HCR than for OPCAB (18/147, 12.2% vs. 22/588, 3.7%; P<0.001). There was no difference in 5-year survival. HCR appears to be a safe and feasible alternative to the OPCAB technique for the treatment of LM and multivessel coronary artery disease. Further investigation into the comparative effectiveness of this minimally-invasive alternative strategy is warranted to identify optimal candidates for HCR.

Conclusion

OPCAB is a valuable skill-set and technique for performing coronary revascularization. Its benefits are most apparent in patients with a higher risk of complications from CPB and aortic manipulation. It should thus be the procedure of choice in patients with advanced ascending aortic disease. Other high-risk subgroups may also benefit and have better outcomes with an off-pump approach. The short- and long-term benefits of OPCAB for patients in all risk categories may be greatest when multiple arterial grafts are used in a surgical procedure that avoids aortic manipulation. This technique requires a unique skill-set, which can be mastered with careful patient selection and experience. However, technical precision, anastomotic quality, and completeness of revascularization should not be compromised in order to avoid CPB, unless these short-term risks outweigh any potential long-term benefit. The adoption of OPCAB techniques in clinical practice provides surgeons with an effective option when CPB and aortic manipulation pose excessive risk to the patient. OPCAB has become the default approach to surgical coronary revascularization at Emory University since 2000. Presently, approximately 90% of all CABG cases are performed without CPB, by a staff of 12 adult cardiac surgeons. Residents are taught OPCAB from the beginning of their training and progress systematically through the performance of various components of the surgical procedure. Finally, the use of minimally-invasive and hybrid approaches has generated much enthusiasm in the surgical and interventional communities, yet these procedures remain technically challenging and more studies and trials are needed to demonstrate their effectiveness.

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