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REVIEW ARTICLE

Off-Pump Coronary Artery Bypass Grafting; is it Still Relevant?

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Abstract: Off-pump Coronary Artery Bypass Grafting (OPCAB) experienced a resurgence in the 1980s -2000s and developed steadily with improvement of the instrumentation and techniques. However questions about graft patency and long-term survival of OPCAB patients still exist. This review attempts to explore the current relevance of OPCAB.

Keywords: CABG, cardiac surgery, OPCAB, coronary artery disease, optimal medical therapy, myocardial revascularization.

1. INTRODUCTION

Coronary Artery Disease (CAD) is the most common mortality cause, which globally accounted for 9 million deaths as recently as in 2015 [1] and by 2020 had risen from 4th place in 1990 to 2nd place in 2019 on the global burden of disease index in all ages [2]. However, in those aged ≥ 50 years, it maintained its prime status as the leading cause of the global burden of disease from 1990 to 2019 [2]. Consequently, the proportion of global Disability Adjusted Life Years (DALY) from ischaemic heart disease increased from 4.7% in 1990 to 7.2% in 2019 [2]. In Africa, a recent study revealed that CAD had a DALY of 1,309/100,000 population with a prevalence of 880/100,000 population [3]. This disease was the 2nd commonest cause of mortality in South Africans in 2010 [4], in the Western Cape Province in 2012 [5] and was ranked the 2nd most common cause of years of life lost (YLL) amongst South Africans [4]. The current prevalence and DALY in South Africa are 1227/100,000 population and 1184/100,000 population, respectively [3].

The management of CAD includes optimal medical therapy (OMT) and myocardial revascularization comprising either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). The choice of treatment modality for the index patient rests mainly with the cardiologist, but more recent guidelines call for the decisions to be made by a team approach (heart team)- consisting of cardiologists and cardiothoracic surgeons based on best medical evidence [6]. There is evidence that CABG has better survival than OMT over a 5 and 10- year period [7].

Cardiopulmonary bypass (CPB) involves blood contact with an artificial surface and on pump CABG (ONCAB) has the additional disadvantage of aortic cross-clamping and reperfusion injury leading to systemic inflammation. Other CPB negative effects, which may contribute to end-organ injury include; non-pulsatile flow, micro-emboli, hypoperfusion and extended CPB duration [8]. The consequences of the CPB induced systemic inflammatory response (SIRS) may include coagulation dysfunction, complement activation and multiple organ dysfunction involving the lungs, brain and kidneys [9].

The quest to evade the CPB deleterious consequences [10] led to a renewal of CABG on a beating heart (also known as "off-pump" CABG or OPCAB) in the mid -1990s. History records Kolesov as a prime initiator of OPCAB in the 1960s [11]. Kolesov was so convinced of the superiority of OPCAB that only 18% of his CABG procedures were performed with CPB and in the late 1970s, he showed excellent patency rates and functional results of CABG [12].

At the onset of OPCAB resurgence, the indications were limited to patients who would benefit the most from the absence of the CPB induced SIRS response and had co-morbidities like porcelain aorta, peripheral vascular disease (PVD) and cerebrovascular disease (CVD); these patients also had single or double vessel CAD [9]. The limitations of the initial OPCAB learning curve included difficulty with exposure of the target vessels, especially the lateral wall and instrumentation at infancy levels of development [9, 10].

The proportion of CABG done as OPCAB increased up to 20-30% in the late 1990s/early 2000s and was due to further developments in anaesthesia and surgical techniques, including improvements in retraction of the heart and exposure of target vessels [9, 10, 13-16]. Some isolated studies showed higher frequencies of OPCAB;20-100% [17-19].

Ideally, OPCAB would be expected to be non-inferior to ONCAB in terms of morbidity, mortality and long-term outcomes and especially for low-income countries, be more economically viable for the development of coronary surgery [8].

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The OPCAB limitations mentioned have included sub-optimal anastomoses quantitatively and qualitatively and the increased risk of intra-operative myocardial ischaemia [8].

This review was conducted to illuminate the role of OP-CAB in coronary artery surgery and explore its relevance.

1.1. Indications

The driving philosophy for OPCAB renewal was the avoidance of the multisystemic deleterious effects of CPB, which included coagulation dysfunction for which the implicated factors composed of consumptive coagulopathy, platelet degranulation, hyperfibrinolysis and haemodilution were induced by excessive CPB priming solution [20]. Secondly, the SIRS effect from CPB has been blamed on activation of complement, endotoxin release, leucocyte activation and liberation of inflammatory mediators [20]. These disorders in concert, cause postoperative bleeding problems and multiple organ dysfunction, including kidneys, brain and lungs [20].

The initial indications for OPCAB were for patients who would derive the most benefit from the absence of CPB; these were high risk patients with severe medical co-morbidities including advanced age, cerebrovascular disease, peripheral vascular disease and religious preferences [9, 20]. It also included those with unclampable/calcified aorta where the risk of stroke would be extremely high from atheromatous or calcific emboli [21]. High risk groups for early morbidity or mortality identified by Chamberlain *et al*., included; age > 75 years, ejection fraction < 30%, recent (< 1 month) myocardial infarction (MI), current congestive cardiac failure, previous CVA, creatinine > 130 µmol/L, current COPD or asthma, peripheral vascular disease, redo surgery and intraoperative endarterectomy [22]. They found an OP-CAB advantage when blood transfusion requirement, intensive care unit (ICU) and hospital stay were considered [22]. On the contrary, the predicted risk of mortality or morbidity in a study by Bakaeen *et al*. was significantly higher for the OPCAB group (13.3% *vs*. 13.1%, P <.001), and this is due to a higher prevalence of noncardiac comorbidities [23].

1.1.1. Targets (Distal Anastomoses)

Several studies show no difference in the number of grafts (distal anastomoses) between OPCAB and ONCAB (3.2 ± 0.97 *vs*. 3.17 ± 0.87; P=0.35) [24]. A similar result was noted in Brazil (OPCAB: 2.8 ± 0.8 *vs*. ONCAB: 2.8 ± 1.2) [18]. Other studies show a lower number of grafts with OPCAB (2.91 *vs*. 3.1; P<0.01) [25] and (3.29 ± 1.09 *vs*. 3.85 ± 0.82; P= .001), but higher number of arterial grafts with OPCAB (1.63 ± 0.91 *vs*. 1.31 ± 0.79; P<.0001) [26].

The reasons adduced for the lower number of OPCAB distal anastomoses include the greater difficulty of performing OPCAB on a beating heart as compared to ONCAB on a still heart and greater associated haemodynamic instability from cardiac manipulation for target vessel exposure [27]. This technical difficulty may negatively influence both patient selection and operative procedural conduct with compromise of the procedure and worse outcomes [28, 29]. Some other studies have also suggested that the fewer OP-CAB grafts are due to patient selection. The study by Magee *et al*. revealed a significantly less mean number of grafts with OPCAB (2.95±1.22) *versus* ONCAB (3.48±1.24) [27], though in this study, the patients that needed more than 3 bypass grafts were more likely to be selected for ONCAB. They introduced the index of complete revascularization (I-CRV), defined as the ratio of bypass grafts divided by the number of angiographically significant lesions to compare the completeness of revascularization between the 2 groups. The ICRV was similar between OPCAB (1.03) and ONCAB (1.07), but they showed that surgeons who perform OPCAB in < 25% of their patients had a significantly lower ICRV in the OPCAB group (0.78) than the ONCAB group (1.09). A significantly worse MACCE was found in OPCAB patients with ICRV < 1 for reasons that were unclear. The conclusion was that ab initio, patients that required fewer grafts were selected for OPCAB and it was not the performance of less than required grafts (leading to incomplete revascularization) that explained the commonly observed lower number of grafts with OPCAB [27].

Some studies have shown a 6.3-29% rate of incomplete revascularization in OPCAB patients [30-32] and one of them showed all the event-free survival for all-cause mortality (p<0.001), cardiac death (p=0.02) and MACCE (p< 0.001) were all lower in those with incomplete revascularization [30].

The right coronary artery (RCA) is grafted less (62.1% *vs*. 73.4%; p < 0.001) and the diagonal arteries (35.7% *vs*. 29.2%; p < 0.001) are more likely to be grafted in OPCAB patients, while there was no difference in the rate of left anterior descending (LAD) artery (98.1% *vs*. 98.7%; p =.24) and circumflex artery grafting (91.8% *vs*. 92.6%; p=.45) [24].

1.1.2. Conduits

The internal mammary artery is used as a conduit in > 95% of OPCAB cases [18, 25]. Early on in the 1980s, it was already proven that the IMA use was associated with increased survival, decreased myocardial infarction (MI) risk, decreased hospitalization risk and a decreased requirement for repeat revascularization [33]. It is also associated with improved early outcomes and reduced early post-operative deaths regardless of the patients' risk status [34]. The use of bilateral IMA (BIMA) is a risk factor for sternal wound infection and is discouraged in patients with co-morbidities like diabetes, COPD and obesity because of the increased sternal wound infection rate in these groups [35], though a paper in 1999 by the Cleveland group confirmed greater survival and reduced requirement for repeat revascularization with BIMA [36].

The radial artery (RA) is a conduit in 3.8-71.4% and 42-58.7% of OPCAB and ONCAB patients, respectively, in several studies [13, 18, 37, 38] with no significant intergroup differences. The RA is versatile and easy to harvest with appropriate length to access all the target vessel territories and uniform luminal calibre along its length [12]. Currently, these merits have placed the RA as the 2nd or 3rd arterial graft of choice [39, 40]. Other advantages of RA include easier and quicker post-operative ambulation, less wound complications and higher short/long-term patient satisfaction [41-43]. On the contrary, RA is prone to spasms and has a higher incidence of intimal hyperplasia and atherosclerosis than the internal thoracic artery [44].

The greater saphenous vein (GSV) graft used in both groups is between 8-77% in both groups [13, 37, 38, 45]. Although CABG originated with arterial conduits, the GSV gained early prominence because of its technical ease of harvest, easy handling and versatility, reproducibility and also the simplification of the operation [12].

The concept of total arterial revascularization (TAR) has been recognized and is encouraged because of the graft patency and survival advantage of arterial over venous conduits. Puskas *et al*. in a 2016 editorial, further emphasized the better long-term graft patency of arterial conduits over venous conduits with respect to survival and adverse cardiovascular events [46]. A randomized study by Deb *et al*. (Radial Artery Patency Study-RAPS) comparing radial artery(RA) and saphenous vein graft (SVG) patency over 5 years postoperatively showed less functional graft occlusion (RA=12%, SVG= 19.7%, p=0.03) and complete graft occlusion (RA=8.9%, SVG=18.6%, p=0.002) in the radial artery [47] . Bilateral internal thoracic artery (BITA) has shown better survival than a single ITA even up to 9 years and also specifically with diabetic patients [46]. The arterial conduits used for TAR include the BITA, RA and right gastro-epiploic artery with different configurations that may include sequential, 'T', 'Y' or 'K' patterns [46, 48].

It must be understood that while TAR is desirable, it is complex in OPCAB with difficulty in exposure and stabilization for the creation of precise anastomoses while concomitantly maintaining haemodynamic stability and avoiding coronary ischaemia [46]. A limited number of conduits may also be a TAR limitation.

Total arterial revascularization (TAR) without the involvement of the aorta and OPCAB has been touted as the optimal strategy for CABG and a study showed anaortic OPCAB was associated with reduced neurologic dysfunction because of the avoidance of aortic manipulation [26]. Tatoulis stated the greater long-term survival at 8 years with TAR (BITA and RA-92%) when compared to LITA and SVG(74%) [48]. He also found fewer reoperations with arterial conduits decreasing from 7% per year (1990-2000) to 3% per year (2005-2008) [48].

1.1.3. Conversion

Conversion from OPCAB to CABG-CPB intra-operatively occasionally occurs for several reasons, which include; anatomic (failure of adequate exposure of target vessel, deep intra-myocardial course of target vessel, small vessels, adhesions or an enlarged heart), haemodynamic instability upon manipulation of the heart (hypotension, mitral and/or aortic regurgitation, bleeding, acute ischaemia as detected by ST segment or wall motion changes, left ventricular dysfunction) and electrical disturbances during the procedure (ventricular fibrillation, ventricular tachycardia, heart block or severe bradycardia [49]. The common target vessels implicated in conversion are the obtuse marginal vessels or the ramus intermedius [37]. Several studies state the conversion rate to be between 0-22.5% [24, 25, 50]. A paper on OPCAB trends in the US over 15 years showing an aggregate conversion rate of 6% with a an increasing rate (1.1% - 2004, 2.6% - 2005, 3.3% in 2012) [23]; The same study showed that conversion rates were highest at low volume OPCAB centres (3.6% [high] *vs*. 6.0% [intermediate] *vs*. 7.3% [low], p < 0.0001) . This increase in conversion rates was adduced to be due to a combination of increasing proportions of complex disease and severe comorbidities, which make them prone to intra-operative haemodynamic instability that leads to conversion [23]. Additional reasons for the increased conversion rate include reduced surgical team experience, low proportion of CABG as OPCAB cases and a rise in the relative percentage of surgeons who do OPCAB intermittently (2.6%[high] *vs*. 6.3% [intermediate] *vs*. 8.4% [low], p <0.0001) [23].

The mortality from intra-operative conversion is increased 6-12-fold than in those without intraoperative conversion [51, 52]. Later studies showed that conversions from OPCAB to ONCAB usually have poor outcomes and are worse with emergency scenarios as Puskas *et al*. and Benedetto *et al*. show a hospital mortality rate of 6.5% and 10.3%, respectively for converted patients [24, 50, 53-55] even with similar frequency of baseline risk factors between converted and non-converted OPCAB patients. This negative effect of conversion persisted at 5-year follow-up [24].

1.1.4. Complications

Preventive and redemptive measures may include identification of predisposing factors enabling recognition of patients at high risk and may include the performance of ONCAB, establishment of lower thresholds for conversion and finally, the institution of targeted monitoring or procedures to reduce conversion risk [23].

1.2. Blood Transfusion

The absence of CPB is postulated to decrease peri-operative blood loss and consequently reduce blood transfusion [56]. The consequences of blood transfusion include transfusion reactions, transmission of viruses (hepatitis B, C, HIV), immunosuppression and increased mortality [20]. The independent risk factors for both single and multiple unit blood transfusion and associated with bleeding induced re-exploration include; advanced age (p<0.01), female gender (p<0.01), increased weight (p<0.01), African ancestry (p<0.01), chronic renal failure (p<0.01), left main stenosis (p=0.02), peripheral vascular disease ([PVD], p<0.01) and re-operative CABG(p<0.01) [20]. Most studies show significantly less RBC usage in OPCAB patients (OPCAB-13.1% *versus* ONCAB-16.5%; p=0.02) [24, 57-59] and some showing no significant difference between the 2 groups. A study revealed the mean number of RBC units transfused is 4± 1.2

units in OPCAB patients and 6.1±3.5 units in ONCAB patients (p=0.15) [60]. A study by Frankel *et al*. showed significantly increased blood transfusion intraoperatively and postoperatively in the ONCAB group (median- ONCAB 874 mls [range 100-10, 500 mls] *vs*. OPCAB 656 mls [range 200-8500 mls], p < 0.001) [20].

1.3. Bleeding

Excessive bleeding plays a key role in the cause of morbidity and mortality after CABG, both from the blood transfusion and the re-exploration [61].

The bleeding in ONCAB postoperatively is initiated by the systemic inflammatory response consequent upon contact with a synthetic, non-endothelialized surface and involves distortions in the coagulation (platelet activation/degranulation and consumptive coagulopathy) and fibrinolytic(hyperfibrinolysis) pathways [20]. Casati *et al*. showed that ONCAB patients underwent transient platelet consumption, increased plasminogen activation and D-dimer formation than OPCAB patients, but 24 hours postoperatively, the coagulative states of both groups became similar [62].

Some studies showed less postoperative and 30-day bleeding with OPCAB (OPCAB=5.1%, ONCAB=5.7%) [17, 63]. One study, however, showed more perioperative bleeding in OPCAB patients, but this could be because a higher heparin dose than usual was used in the OPCAB patients studied [49].

Different modalities are available to ameliorate intraoperative and postoperative bleeding in both groups of patients; These include ultrafiltration (intraoperative), tranexamic acid, arginine vasopressin, corticosteroids. All these measures aim to decrease the SIRS response associated with the CPB use [20].

1.4. Atrial Fibrillation

Postoperative Atrial Fibrillation (AF) can cause thrombo-embolic complications, additional medication, increased cost, increased hospital stay and in those burdened with failure of electrical conversion, they have the prospects of anticoagulation and its attendant risks [64-66]. Some studies showed less postoperative AF with OPCAB(OR,0.88; p <0.001) [67]. This finding was echoed by a 2004 article that showed the presence of postoperative AF to be 19% and 24% in OPCAB and ONCAB patients, respectively (OR=0.69, p=0.02) [68].

1.5. Neurological Complications

Neurologic complications after CABG are associated with increased morbidity, mortality, longer hospitalization and increased costs [69].

Neurological dysfunction has types 1 (stroke, coma) and type 2 (cognitive dysfunction); while type 1 is a cerebro-vascular accident (CVA) and may be transient or permanent, type 2 is due to fluctuations in cerebral perfusion during CPB, may also be transient with > 60% recovery over 6 months and about 30% persistence [70].

Several reports have shown no difference in perioperative, short-term, 1-year and 5-year stroke rates between OPCAB and ONCAB patients [24, 63, 71-75]. Other studies have shown better neurocognitive outcomes and stroke rates with OPCAB [17, 25, 50, 67, 76-78].

The neurological dysfunction is seen post CABG may be due to micro-embolic load and cerebral hypoperfusion in addition to the effects of CPB [79]. More specifically, these cerebral emboli are released from ascending aorta atheroma during aortic cannulation for arterial inflow or antegrade cardioplegia and clamping (partial or full) for proximal conduit anastomosis [21, 72, 80]. Even within the OPCAB group, avoidance of aortic manipulation showed better stroke rates [71]. Significant macro and micro emboli production as revealed by transcranial Doppler ultrasonography occurs during ascending aortic cannulation and all the clamping types (full or partial) or processes (removal or adjustment) and are linked to significant neurologic dysfunction post CABG [21].

The avoidance of clamping in OPCAB is associated with a statistically significantly decreased risk of stroke when compared to ONCAB (0.38% *vs*. 1.87%, p <0.001) and also when compared to OPCAB with a partial clamp (0.31% *vs*. 1.35%, P=0.001) [81]. Another study that compared clampless OPCAB with ONCAB showed a 44% statistically significant decrease in 30-day stroke rates with OPCAB [71].

Avoidance of aortic manipulation in OPCAB patients (aortic manipulation-1.4%, anaortic-0.4%) is associated with a statistically significant less frequency of postoperative neurologic complications [82]. A combination of OPCAB and total arterial revascularization, the so-called aortic no-touch technique has been put forward as an excellent strategy to reduce neurologic complications in CABG [83, 84] (reduction of stroke of 0.8% *vs*. surgical arm of the syntax trial-2.2%). The efficiency of this technique was found to be both safe and effective [85-87] and led to less neurologic complications even in high -risk patients [26]. It must also be realized that the etiology of neurologic dysfunction in 3% of CABG patients is multifactorial and may not be avoided by the reduction of aortic manipulation alone [69].

The use of anastomotic devices in addition to aortic no touch OPCAB with total arterial revascularization has also been touted to reduce neurologic complications [26, 82, 88] especially in patients with a high atherosclerotic burden.

1.6. Renal Failure

There is an early mortality increase (7-38%) associated with postoperative renal failure in both ONCAB and OPCAB patients [89-91], with an additional mortality increase (up to 60%) in those that require dialysis (1-5%) [92]. The markers of renal dysfunction (creatinine clearance, micro-albuminaria, urinary N-acetyl-β-glucosaminidase) are all significantly worse in ONCAB patients because of the CPB effect [91, 93, 94]. The factors implicated in negative CPB renal effect include SIRS, absence of pulsatile flow, haemodilution, low-output syndrome, increased catecholamine and free haemoglobin levels [95, 96].

Some studies show nil difference in postoperative (OPCAB-2.3% *vs*. ONCAB-2.4%) [17], 1-year (OPCAB=1.3%, ONCAB=1.3%) [74] and 5-year renal failure (OPCAB=1.7%, ONCAB=1.9%, P=0.6) [75] between OPCAB and ONCAB patients. Other reports show less in-hospital, 30-day and short-term postoperative renal failure rates (OR= 0.74, P<0.001) and renal replacement therapy (OR= 0.63, P <0.001) in OPCAB patients [24, 63, 67, 78].

1.7. Perioperative Myocardial Infarction

Perioperative myocardial infarction (PMI) is seen in 0.35-4% and 0.4-3% in OPCAB and ONCAB patients, respectively [14, 38, 97-101] with some showing statistically significantly lower rates in OPCAB patients [10, 24, 67]. Other studies showed no difference in MI rates at 30 days (OPCAB-4.31%, ONCAB-4.67%, P=0.19) [25], 1 year [73, 74] (OPCAB= 6.8%, ONCAB=7.5%) and at 5 years (OPCAB= 3%, ONCAB=4.1%, P=0.06) [24] (OPCAB= 7.5%, ONCAB=8.2%, P=0.41) [75].

The markers of myocardial damage; creatinine kinase-myocardial band (CK-MB) and troponin T levels in some studies were significantly lower postoperatively in the OPCAB group [59, 60, 102, 103]. A 2003 study showed a 41% reduction of CK-MB release from OPCAB patients as compared to ONCAB patients [104], while another study showed a lower CK-MB peak at 24 hours postoperatively [24].

1.8. Death

Many studies in the early 2000s failed to show significant differences in perioperative mortality between OPCAB and ONCAB, with figures of 0-2.6% and 1-3.3% being quoted [8, 17, 18, 104], while more recent studies had similar findings (OPCAB-1%, ONCAB-1.2%; P=0.7) [24]. Some examples of these include the Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2), which were two single-centre randomized trials carried out at the Bristol Heart Institute on a total population of 401 (200 off-pump) elective patients [105]. Many other studies also showed less hospital mortality [106] (2.3% *versus* 2.9%) [29, 67, 107] in OPCAB patients.

The 30-day mortality was similar between the 2 groups in some studies including the CABG Off or On Pump Revascularization Study [CORONARY] trial of 4752 patients with mixed operative risk profile (OPCAB= 2.04%, ONCAB=2.45%, P=0.25) [25, 63, 73, 108] and less with OPCAB in others [78] and in one showing a 56% significant reduction [71].

Short-term (1-1.5 year) mortality after OPCAB and ONCAB were similar in several studies [73], (OPCAB= 5.1%, ONCAB=5%) [74] and (OPCAB= 9.4%, ONCAB=6.7%, p=0.15) [27].

Similar results were seen in 5-year mortality between the groups (OPCAB= 14.6%, ONCAB=13.5%, P=0.3) [75] (OPCAB= 8.9%, ONCAB=8.3%, P=0.35) [24] and also no difference in cardiovascular deaths between the groups at 5 years (OPCAB=10%, ONCAB=9.7%, P= 0.69) [75] and (OPCAB-4.1% *vs*. ONCAB-3.1%, P=0.13) [24] .

However, other studies have revealed more 5-year mortality rates in OPCAB *versus* ONCAB patients (15.2% *vs*. 11.9%, relative risk-1.28, P= 0.02) [109]. Long-term all-cause mortality (≥ 5 years) was 7% significantly higher in OPCAB than in ONCAB patients (HR, 1.07; 95% CI, 1.03-1.11; P= 0003) [110]. This worse survival with OPCAB could be explained because of the less distal anastomoses [81] and the graft patency rate [111]. Takagi *et al*. showed a 37% decrease in long-term mortality in patients with complete revascularization when compared to those with incomplete revascularization, an effect more pronounced in multivessel disease and diabetes [112].

The identified risk factors for mortality include; intra-operative conversion from OPCAB to ONCAB [113], age, female gender, carotid artery disease, chronic renal failure, low LVEF, pre-operative intra-aortic balloon pump (IABP) and recent MI [114, 115].

1.9. Risk Scores and Mortality

Knowledge of the patient categories that may derive maximal benefit from OPCAB could affect the use of OPCAB for that category.

There is ample evidence of OPCAB being the most suitable in those with higher risk scores. Several studies, as outlined below, show this.

The benefits of OPCAB on mortality seem to be seen in those with high predicted risks of mortality [59, 116]. These studies showed a cut-off of (European System for Cardiac Operative Risk Evaluation score > 4.5 or 2000 Bernstein--Parsonnet score >17.75) for a significantly reduced chance of operative mortality with OPCAB and 5.4x chance of death with ONCAB [116]. This benefit with OPCAB was found to be absent in those with lower surgical risk [117, 118]. For a given value of the Euroscore, the ONCAB patients had 2x chance of death than OPCAB patients and for each unit Euroscore increase, also had 1.4X increased risk of death [116]. Lemma *et al*. showed in their study of 411 high--risk patients (Euroscore ≥ 6, mean =8) that the composite primary end-point (operative mortality, MI, stroke, renal failure, reoperation for bleeding, p=0.01) was significantly less in the OPCAB group and the likelihood to have one of the primary end-points was significantly higher in ONCAB patients (odds ratio, 3.07; 95% confidence interval, 1.32-7.14; P=.009) [119]. A large observational study of > 80,000 patients showed a significantly less postoperative stroke in high risk patients who had OPCAB [120]. Some observational studies that compared OPCAB and ONCAB may have been skewed towards recruitment of higher-risk patients in the OPCAB group [24].

The study by Puskas *et al*. showed the patients in the highest risk quartile (STS PROM ≥ 2.5%) had a statistically significant decrease in hospital mortality with OPCAB when compared to ONCAB (3.2% *vs*. 6.7%, P < 0.0001) [118]; patients with an STS predicted risk of mortality (PROM) >

2.5% had a survival advantage with OPCAB, with the benefit being most significant with STS PROM >3%. The same study showed there was no significant difference in observed mortality between OPCAB and ONCAB for patients in the lower 2 risk quartiles (STS PROM 0-.75% and 0.75-1.3%) [118]; a finding also echoed by Borgemann *et al*. [121]. A study (retrospective observational) showed an increase in mortality and stroke rates in both OPCAB and ONCAB as the STS PROM increases, yet all the PROM quartiles revealed less mortality rates in OPCAB patients [59]. The OPCAB percentage in the lowest and highest PROM groups were 20.8% and 25.8%, respectively [59].

The reasons for the touted advantage of OPCAB in high--risk patients remain controversial. It has been suggested that the avoidance of CPB and interactions between the inflammatory, coagulation and fibrinolytic systems confers complex, organ -specific benefits, especially in high-risk patients [25]. Yokohama *et al*. showed a significantly less mechanical ventilation in COPD patients that had OPCAB and suggested the effect was because of the absence of negative fluid shifts and SIRS secondary to CPB in a dysfunctional respiratory system; Operative mortality was 0% in the OPCAB group as against 2.3-8.3% in the ONCAB groups [122].

1.9.1. Long-term Follow-up

Many studies have shown inferior graft patency with OPCAB [29, 103, 123]. However, results from units with OPCAB expertise reveal equivalent graft patency between the 2 groups [101, 124]. The use of mechanical stabilizers and intracoronary shunts improved the quality of anastomoses and the completeness of revascularization [125].

1.10. Graft Patency

A meta-analysis showed a statistically significant higher rate of postoperative graft occlusion in OPCAB (14.6%) than ONCAB (10.7%) groups (RR, 1.35; 95% CI, 1.16-1.57) [111]; this was equivalent to a 35% increased rate of graft occlusion in conduits in OPCAB when compared to ONCAB. Further analysis showed this finding was driven mostly by saphenous vein graft (SVG) occlusion in OPCAB (22.5%) *versus* ONCAB (16.4%), while there were no significant differences between OPCAB and ONCAB when the LIMA graft (OPCAB-5.7%, ONCAB-5% RR, 1.15; 95% CI, 0.83-1.59), and radial artery grafts (OPCAB-12.1%, ONCAB-7.4% RR, 1.37; 95% CI, 0.76-2.47) were considered [111]. This finding suggested that arterial graft patency is preserved when OPCAB is compared to ONCAB. The SVG occlusion could be acute (technical failure or thrombosis) or late (atherosclerosis or generalized intimal hyperplasia) [126].

The reasons adduced for the lower OPCAB graft patency include a more challenging OPCAB anastomosis because of the beating heart and a hypercoagulable state seen postoperatively in OPCAB [127, 128]. A study by Uva *et al*. actually showed significantly less OPCAB graft patency (OPCAB-89.9%, ONCAB-95%, OR 2.2, 95% CI 1.07-4.44; p=0.03) which was absent after adjustment for differing heparin doses between the ONCAB and OPCAB (OR 0.87, 95% CI 0.25-2.98, P =0.83) [129]. Another study found that a significant reduction in fibrinogen concentration after ONCAB compared to OPCAB predisposed the OPCAB grafts to a higher risk of occlusion [130]. This led to the suggestion that delayed institution of subcutaneous enoxaparin or dual-antiplatelet therapy in the early postoperative period could lead to decrease of early graft patency in OPCAB patients [111].

In the DOORS study, there were fewer OPCAB grafts globally and regionalized in all coronary artery territories [49]. The graft patency (6-month postoperative angiography) in ONCAB was significantly better, though the patency of anterior territory grafts was similar between the 2 groups, but worse in circumflex and right coronary artery territories in OPCAB patients. The proportion of nonoccluded left internal thoracic artery grafts was 95% in both groups, with higher proportions of stenotic and occluded vein grafts and grafts of the radial artery or right internal thoracic artery [49].

Graft occlusion may be caused by hypercoagulability but is more likely caused by technical anastomotic issues, with the experience of the surgeon being an important factor [49]. As previously stated, the construction of a beating heart lateral wall (circumflex territory) coronary artery anastomosis is more technically challenging and needs a longer learning curve [131]. After accounting for adequate surgeon experience, the less graft patency of OPCAB has been adduced to be due to the inherent weakness of the procedure [49].

1.11. Major Adverse Cardiac, Cerebral Events (MACCE)

Major adverse cardiac event (MACCE) comprises the following: angina, congestive heart failure, percutaneous coronary intervention, arrhythmia, sudden death and Cerebro-Vascular Accidents (CVA).

There were similar recurrent angina rates at 1 year between the 2 groups (OPCAB=1%, ONCAB=0.9%) [74] and at 5 years between the 2 groups (OPCAB=1.7%, ONCAB=1.6%, P=0.81) [75]. There were also no significant differences in recurrent angina rate in a meta-analysis [132].

For the other MACCE components, mid-term and long-term events for MI, heart failure and CVA were similar between the 2 groups [81, 132]. Other studies echoed this; No difference in 18 month MI rates between the groups (OPCAB= 0.9%, ONCAB=2%, p=0.38) [27] and no difference in 18 month MACCE rates between the groups (OPCAB= 15.5%, ONCAB=14.1%, p=0.57) [27]. On the contrary, the study showed a combined 2-year MACCE (mortality, stroke, MI) rates lower with OPCAB (3.1%) *versus* ONCAB (4.4%) [67].

Longer term studies revealed no difference in MACCE between the groups at 5 years (OPCAB=14.3%, ONCAB=13.8%, P= 0.65) [24], while others showed more 5-year MACCE rates in OPCAB *versus* ONCAB patients (31% *vs*. 27.1%, relative risk, 1.14; 95% CI, 1.00-1.30;

P=0.046) [109]. Criticisms of this study by Shroyer *et al*. was the 53 participating surgeons enrolled a mean of 8 patients per year, had high rates of conversion (12%) and incomplete revascularization (18%) and a trainee surgeon was the primary surgeon in 60% of the case with the suggestion that relative inexperience translated to poor graft patency [24].

1.12. Re-intervention

Repeat revascularization rates mid-term and long-term were shown to be similar in a 2014 meta-analysis [132] and other studies [81].

Conflicting reports showing nil difference in in-hospital repeat revascularization rates between OPCAB and ONCAB (0.6% *vs*. 0.6%, P=1) [24] and higher rates of repeat revascularization (PCI or CABG) at 30 days in OPCAB patients [63].

Short-midterm studies (1-1.5 years) showed similar 1-year revascularization rates between the 2 groups [73], (OPCAB=1.4%, ONCAB=0.8%) [74] and at 18 month (OPCAB=5.5%, ONCAB=5.7%, p=0.9) [27].

Long-term studies (CORONARY Trial) reveal no difference in 5-year revascularization rates between the groups (OPCAB=2.8%, ONCAB=2.3, P=0.29) [75]. There were also similar repeat revascularization rates between groups if it was either PCI (OPCAB=2.5%, ONCAB=2.2%, P=0.48) or CABG (OPCAB=0.4%, ONCAB=0.2%, P=0.17) as a revascularization strategy at 5-year follow-up [75]. Other studies support this with no difference in 5-year revascularization rates between the groups (OPCAB=7.5%, ONCAB=6.8%, P=0.58) [24].

Many studies have shown higher rates of repeat revascularization with OPCAB [29, 103, 123]; Statistically significant 38% increase in repeat revascularization rates with OPCAB *versus* ONCAB (odds ratio, 1.38; 95% CI, 1.09-1.76; P=0.008) [133].

The ROOBY trial showed a similar rate of repeat revascularization (OPCAB-13.1%, ONCAB-11.9%; P=0.39), but a higher rate of repeat CABG (OPCAB-1.4%, ONCAB-0.5%; P=0.02) [109].

The repeat revascularization frequency may be affected by the factors discussed above, *e.g.,* graft patency, completeness of revascularization and the higher technical challenge of OPCAB leading to inferior graft patency, incomplete revascularization and subsequent revascularization [132].

1.13. Quality of Life

A study showed a small decline in the quality of life in both groups at the time of hospital discharge as measured with the European Quality of Life-5 Dimensions questionnaire (EQ-5D) and the EQ-5D visual-analogue scale. This decline was followed by a sharp increase in both ONCAB and OPCAB groups at 30 days and 1 year with similar results between the groups at any time point [74]. There were also similar results between the groups at 5 year follow-up with both the EQ-5D and EQ-5D visual analogue scales [75]. This is a testament to CABG as a worthy procedure because the increase in quality of life observed after surgery was maintained till the 5-year follow-up.

1.14. Neurocognitive Function

There was less reduction from baseline in neurocognitive function (Digit Symbol Substitution Test) in the OPCAB patients than the ONCAB patients (P=0.04) at hospital discharge, but similar results between the groups at 30 days and 1 year [74]. Other tests are done in this study using the Montreal Cognitive Assessment (MOCA) or the Trail Making Test Part B also showed similar results between the groups at 1 year [74].

1.15. Cost

The attraction of OPCAB for low/middle income countries is the cost-effectiveness with savings of about 25% per patient when compared to ONCAB being quoted [134]. Other studies showed reduced costs with OPCAB [103, 124, 135, 136].

However, a randomised controlled trial did not show any significant difference in mean cost per patient between the OPCAB and ONCAB groups at 5-year follow-up (OPCAB= $15,107, ONCAB=$14,992, US Dollars 2016) [75]. There was also no significant difference between the 2 groups at any time point during the trial, or in any category of costs-procedures, events, medications, ICU stay or ward stay [75]. These cost figures reflected the results of the primary analysis of the data from this study. However, a major limitation was that the specific costs of the OPCAB retractors and the cardiopulmonary bypass circuits were not included [75]. There is a suggestion that since some OPCAB retractors are reusable and CPB circuits used with ONCAB are not, some cost savings may accrue with the OPCAB technique [75].

2. SPECIAL POPULATIONS

2.1. Elderly

The German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) study focused on patients 75 years of age or older [137]. The mean number of distal anastomoses in the OPCAB group was significantly less than that in the ONCAB group (2.7 *vs*. 2.8, p < 0.001) [137]. The reasons for conversion from OPCAB to ONCAB in this study were haemodynamic instability, highly calcified coronary arteries and inadequate target vessel exposure. At 30 days and 12 months, there was no significant difference in the composite endpoints of death, stroke, myocardial infarction, repeat revascularization or new renal replacement therapy between the 2 groups [137]. However, the OPCAB group had a higher repeat revascularization rate within 30 days (1.3% *vs*. 0.4%, P=0.04). The OPCAB group had less packed red blood cell transfusion than the ONCAB group, but the operative time, duration of mechanical ventilation, length of ICU stay and length of hospital stay were similar between the 2 groups [137].

The Danish On-pump *versus* Off-pump Randomization Study (DOORS) study [49] showed similar 6-month mortality rates between OPCAB (4.2%) and ONCAB (4.7%) in elderly patients. There were fewer OPCAB grafts even present in all coronary artery territories. The graft patency in ONCAB was significantly better, though the patency of anterior territory grafts was similar between the 2 groups but worse in circumflex and right coronary artery territories in OPCAB patients.

Another study suggested the benefits derived from OPCAB will be evident in the high-risk patients like the elderly with a high atherosclerotic burden [118].

2.2. Diabetes Mellitus Patients

The patients with diabetes mellitus account for about 25% of all patients who have coronary revascularization procedures yearly [138] and it's known that CABG is associated with better outcomes in DM patients when compared to percutaneous coronary intervention (PCI) [139] with current guidelines suggesting CABG as the preferred strategy for DM patients with multi-vessel disease [6].

There is conflicting evidence about the role of OPCAB in the management of DM patients. A study (Bypass Angioplasty Revascularization Investigation 2 Diabetes trial) suggested DM patients had a greater risk of MACCE after OPCAB than ONCAB [140]. However, this study was said to be limited by a small sample size and incomplete information on completeness of revascularization which precluded definitive conclusions.

Another study of CABG in DM patients showed less number of grafts, less saphenous vein usage, more incomplete revascularization (absolute 7% increased risk) and more radial artery usage with OPCAB [141]. The OPCAB patients with incomplete revascularization had significantly less survival than OPCAB patients with complete revascularization and ONCAB patients with complete revascularization [141]. There is some evidence that suggests that DM patients are more likely to benefit from complete revascularization with up to 10% less mortality with complete revascularization [112, 142].

Short term outcomes including postoperative CVA, need for postoperative IABP, re-exploration for haemorrhage and sternal wound reconstruction were all less with OPCAB with similar 30-day mortality between the 2 groups [141, 143].

There was also similar 5 and 10-year mortality rates between the 2 groups (p=0.32) [141].

2.3. Surgical Volume

Mortality and complications were found to decrease as the proportionate use of OPCAB in a hospital increased [17, 144]. This study [17] showed that for hospitals in the highest quartile of percent OPCAB, the risk of in-hospital mortality and complications were 50% and 27% lower, respectively, than for ONCAB (p< .001) They also suggested that the proportion of CABG procedures performed as OPCAB may be more important than the actual volume of OPCAB done in a hospital. This suggests that some hospitals may specialize in OPCAB expertise and that the achievement of a certain level of skill is essential for the achievement of better outcomes. Lapar at al showed an estimated 5% decrease in risk of death among OPCAB patients when done by surgeons with the highest volume as compared with a 3% decrease in ONCAB patients [144]. The same study showed the greatest benefit in mortality occurs after 50 OPCAB operations annually and the lowest risk of death was seen with surgeon volumes of ≥ 150 OPCAB procedures annually [144].

The ART trial showed that cases performed by surgeons with 1-5 OPCAB procedures had a high conversion rate (12.9%), a lower number of grafts (2.6 ± 0.88) and a higher rate of mortality (4.8%) compared with other OPCAB subgroups regardless of the fact that the risk factor distribution was similar [24]. There was no significant difference in 5-year mortality and MACCE rates between OPCAB procedures performed by 3 OPCAB surgeons who performed > 60 procedures when compared to ONCAB procedures performed by 95 "ONCAB only" surgeons [24]. Surprisingly, the 28 ONCAB cases performed by these 3 OPCAB surgeons (> 60 procedures) above had a high hospital mortality rate (7.1%); the explanation for this was the high prevalence of LVEF < 30% and increased creatinine compared to other ONCAB categories suggesting that these 3 surgeons preferred ONCAB for high-risk patients [24].

A study showed that surgeons who use OPCAB in < 25% of CABG patients had a significantly less index of complete revascularization (ICRV) in the OPCAB patients (OPCAB=0.78, ONCAB=1.09) and those with >25% of CABGs done as OPCAB were equally likely to achieve complete revascularization regardless of whether OPCAB or ONCAB was used [27]. The use of OPCAB in high volume centres was also associated with significant decrease in risk of stroke, acute renal failure and prolonged hospital stay [59].

Other studies have also demonstrated no differences in OPCAB outcomes between high volume and low volume centres [145-147]. Some authors have opined that the reason for the volume-outcome association for OPCAB is selective referral, that is, patients who are good candidates for OPCAB are selectively referred to centres with good OPCAB pedigree [146]. The applicability and generalizability of results from RCTs comparing OPCAB to ONCAB should be cautious as some previous studies recruited from centres that performed above -average percentages of OPCAB [148].

2.4. Incidence/Usage During Different Eras

The paper by Bakaeen *et al*. showed a 1st OPCAB peak at 23% in 2002 followed by a slow decline to 19% in 2006, a 2nd peak of 21% in 2008 and then a decline to 17% in 2012 in the US. The clinical trials which espoused the advantage of ONCAB over OPCAB may be responsible for this decline, in addition to organizational and surgeon dissatisfaction with the procedure and organizational reduction in OPCAB use by centres that had hitherto used it often [23]. From a different perspective, the use of OPCAB also significantly increased from 15.3% in 2000 to 21.1% in 2004 in the USA [17]. The OPCAB usage upsurge during its peak periods might be due to increased patient demand as both ONCAB and OPCAB may be viewed to be equally invasive since both are traditionally done *via* a sternotomy access [23].

As stated above by Lapar *et al*, centres who perform OPCAB more frequently have better morbidity and mortality results [144]. There are hospitals where mortality rates and complications declined with increased OPCAB proportions [17].

The criticism of some published clinical trials is the recruitment of principally low risk patients, a situation which may fail to show the benefits of OPCAB seen in high-risk patients operated on by the those with more OPCAB expertise. In addition, multi-centric studies that encompass both high and low volume centres participating in clinical trials and observational studies are less likely to reflect the OPCAB advantages than those by surgeons who almost exclusively perform OPCAB [149]. Data of effect of hospital administration and processes on OPCAB usage is usually not obtained or reported in clinical trials and this may be an impactful factor on OPCAB usage [17].

The concerns with graft patency and completeness of revascularisation with OPCAB may also affect its usage [123].

In Brazil, OPCAB utilization increased from 3% in 1991, 10% in 1993, 72% in 1995 and about 95% in 2003 [18].

CONCLUSION

The OPCAB procedure has had a chequered history with peaks of usage and was initially viewed as an outlet for the portrayal of surgical skill, but with the development of instrumentation for improvement of target vessel exposure and heart stabilization, its use has become more widespread and accepted [8].

It is safe to say OPCAB can be done with outcomes similar to ONCAB but by those experienced (with a high frequency of use) and committed to the technique [150].

The mastery of the OPCAB techniques requires a significant learning curve and to avoid poor postoperative outcomes, strategies involving appropriate patient selection, adequate training and gradual incorporation of more complex cases are recommended [151]. As an investment in the future generations of surgeons, trainee surgeons can be safely trained and guided in OPCAB techniques and still avoid negative outcomes [152].

Discussion of the differences between OPCAB and ONCAB has to be nuanced because of heterogenous results derived from observational and randomized studies. These differences arise from differences in the number of patients, risk stratification, presence of co-morbidities, number of distal anastomoses (and by extension long-term outcomes) and even volume of OPCABs done by the participating surgeons.

Current evidence suggests that both techniques (OPCAB and ONCAB) have excellent safety and efficacy profiles and the relevance of OPCAB is assured.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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