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Review

# The present status of off-pump coronary artery bypass grafting

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**Summary**

Coronary revascularisation using cardiopulmonary bypass remains the gold standard treatment for coronary artery disease. Over the past decade, techniques of revascularisation on the beating heart without the use of cardiopulmonary bypass (off-pump surgery) have evolved with an attempt to reduce the potential deleterious effects of extracorporeal circulation. Several trials have reported a significant reduction in morbidity with avoidance of cardiopulmonary bypass, while large observational studies have also reported a reduction in mortality. Complete avoidance of aortic manipulation by using off-pump techniques and composite grafts may add an additional benefit particularly in patients at highest risk of stroke. The impact of this mode of revascularisation has probably been underestimated especially in an era where surgical revascularisation is being increasingly undertaken in older patients with significant comorbidities. In this contribution, the current evidence from randomised trials, meta-analyses and observational studies is critically reviewed.


*Keywords:* Coronary artery bypass grafting; Cardiopulmonary bypass; Off-pump

## 1. Introduction

Conventional coronary artery bypass grafting (CABG) using cardiopulmonary bypass and cardioplegic arrest has been the gold standard treatment of ischaemic heart disease for several decades. It provides the surgeon with a still bloodless operating field allowing effective myocardial revascularisation and coronary reconstruction while providing adequate myocardial protection. Currently, around 600,000 CABG procedures are performed worldwide. CABG is the most extensively studied surgical procedure ever undertaken with follow-up data extending to over 20 years. It is highly effective in relieving the symptoms of IHD and improving life expectancy in certain anatomic patterns of disease; these benefits are magnified in patients with more severe disease and in those with impaired left ventricular function [1]. Furthermore, CABG is a remarkably safe therapy. Improvements in medical, anaesthetic and surgical management have ensured that its mortality has remained around 2% over the last decade despite the fact that it has been increasingly applied to an ageing and sicker patient population. The main drawback of CABG in the long term is vein graft failure leading to recurrent angina, myocardial infarction and death. However, the widespread use of antiplatelet agents and statins may improve graft longevity. More importantly, the use of more arterial grafts appears to improve long-term outcome [2].

### So with such safe therapy, why change practice?

The introduction of extracorporeal circulation in the 1950s has revolutionised the practice of modern cardiac surgery. While it remains essential in most cardiac operations it has several disadvantages. First, its use is associated with a systemic inflammatory response syndrome (SIRS), due to activation of a myriad of cellular and humoral inflammatory mediators, as blood circulates through the extracorporeal circuit [3]. This systemic inflammation can potentially cause multi-organ dysfunction and subsequent failure. Second, cardiopulmonary bypass (CPB) has been regarded as an important aetiological factor in the generation of particulate and gaseous microemboli which can further contribute to end organ damage. Despite these limitations, it is still very widely used as a large proportion of cardiovascular surgical procedures can only be performed using CPB.

In an attempt to ameliorate the potential deleterious effects of CPB, avoidance of cardiopulmonary bypass has evolved over the last decade as a new strategy in surgical revascularisation. Kolessov [4] reported the first experience with coronary artery surgery on the beating heart in 1967, but the technique was soon abandoned with the increasing availability of CPB. However, off-pump CABG has experienced a recent revival, beginning in the early 1990s with the work of Benetti and colleagues [5] and Buffolo and colleagues

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[6]; their work in South America was motivated by economic considerations, but demonstrated that unexpected benefits may be associated with the avoidance of CPB. It is estimated that about 20–25% of CABG is now performed off-pump, and the proportion is likely to increase [7,8]. There is a geographical discrepancy in the application of off-pump surgery. In Asia, the majority of CABG cases are performed off-pump which is markedly different from the Western world where off-pump contributes to 15–20% of CABG procedures. The reason for this is multifactorial but may reflect political and economic considerations as well as clinical indication.

Hypothetically, off-pump surgery would be expected to result in a reduction in systemic inflammation and subsequent end-organ dysfunction as well as avoidance of myocardial ischaemia. The evidence for off-pump surgery comes from three sources: systematic reviews and meta-analyses, observational studies, and randomised controlled trials. These are reviewed here in detail.

## 2. Evidence from meta-analyses

Several meta-analyses have been conducted comparing outcomes of revascularisation with and without cardiopulmonary bypass (Table 1). These generally reported improved or at least equivalent outcomes with off-pump compared to on-pump surgery especially with regards to postoperative mortality, stroke, myocardial injury, atrial fibrillation, need for transfusion and hospital stay [9–13]. However, an important qualification regarding most of these studies is that they were performed in highly select and relatively low-risk patient groups, where mortality and morbidity rates were already low. In large observational studies, reflecting a more realistic and 'real life' situation, the benefits of off-pump CABG appear greater [14–17].

A scientific statement from the American Heart Association council on cardiovascular surgery and anaesthesia in collaboration with the interdisciplinary working group on quality of care and outcomes research state that patients may achieve an excellent outcome with either type of procedure, and individual outcomes likely depend more on factors other than whether they underwent standard CABG or off-pump CABG [18]. Nevertheless, there appear to be trends in most studies. These trends include less blood loss and need for transfusion, less myocardial enzyme release up to 24 h, less early neurocognitive dysfunction and less renal insufficiency after off-pump surgery. Fewer grafts tend to be performed with off-pump than with standard CABG. Length of hospital stay, mortality rate, and long-term neurological function and cardiac outcome appear to be similar in the two groups.

Cheng and colleagues carried out a meta-analysis of 37 randomised trials (3369 patients) of off-pump vs on-pump CABG [11]. No significant differences were found for 30-day mortality, myocardial infarction, stroke, renal dysfunction, intra-aortic balloon pump use, wound infection, re-exploration, or re-intervention. However, off-pump surgery was associated with a significant reduction in the rate of atrial fibrillation, transfusion, inotrope requirements, respiratory infections, ventilation time, intensive care unit stay, and hospital stay. Patency and neurocognitive function results were inconclusive. In-hospital and 1-year direct costs were higher for conventional surgery. Therefore, this meta-analysis demonstrates that mortality, stroke, myocardial infarction, and renal failure were not reduced with off-pump CABG, however, selected short-term and mid-term clinical outcomes and resource utilisation were improved compared with on-pump surgery.

Another meta-analysis of 37 randomised controlled trials (RCTs) ($n = 3449$) and 22 risk-adjusted (logistic regression or propensity-score) observational studies ($n = 293{,}617$) was conducted by Wijeysundera and colleagues [19]. In RCTs, off-pump was associated with reduced atrial fibrillation and trends toward reduced 30-day mortality (OR: 0.91; 95% CI: 0.45–1.83), stroke (OR: 0.52; 95% CI: 0.25–1.05), and myocardial infarction (OR: 0.79; 95% CI: 0.50–1.25). In contrast, observational studies showed off-pump to be associated with reduced 30-day mortality (OR: 0.72; 95% CI: 0.66–0.78), stroke (OR: 0.62; 95% CI: 0.55–0.69), myocardial infarction (OR: 0.66; 95% CI: 0.50–0.88), and atrial fibrillation (OR: 0.78; 95% CI: 0.74–0.82). At 1–2 years, off-pump was associated with trends toward reduced mortality, but also increased repeat revascularisation (RCT: OR: 1.75, 95% CI: 0.78–3.94; observational: OR: 1.35, 95% CI: 0.76–2.39). The authors thus concluded that randomised controlled trials did not find, aside from atrial fibrillation,

Table 1
Summary of meta-analyses comparing on-pump and off-pump surgery.

| Study | Number of patients | Meta-analysis | Main outcomes (off-pump vs on-pump) |
|---|---|---|---|
| Reston and colleagues [13] | 39,647 | RCTs and observational studies | Reduced hospital stay, operative morbidity and mortality |
| Van der Heijden and colleagues [12] | 1584 | RCTs | OPCAB equivalent to conventional CABG |
| Cheng and colleagues [11] | 3369 | RCTs | Reduction in the rate of atrial fibrillation, transfusion, inotrope requirements, respiratory infections, ventilation time, intensive care unit stay, hospital stay and cost |
| Parolari and colleagues [10] | 1105 | | Reduced postoperative graft patency with OPCAB |
| Wijeysundera and colleagues [19] | 293,617 | RCTs and observational studies | RCT: reduced atrial fibrillation and trends toward reduced 30-day mortality and MI Observational studies: reduced 30-day mortality, atrial fibrillation, stroke and myocardial infarction, but increased repeat revascularisation rate at 1–2 years |
| Moller and colleagues [20] | 5532 | RCTs | Reduced AF but similar mortality, myocardial infarction, stroke, and renewed coronary revascularisation rates |

RCT: randomised controlled trial.

statistically significant reductions in short-term mortality and morbidity demonstrated by observational studies. These discrepancies might be due to differing patient selection and study methodology. Future studies must focus on improving research methodology, recruiting high-risk patients, and collecting long-term data.

Most recently, a meta-analysis by Moller and colleagues that included 5532 patients from 66 trials reported no benefit of off-pump vs on pump surgery with respect to mortality, myocardial infarction, stroke, and renewed coronary revascularisation [20]. However, they demonstrated a significant reduction in the rate of atrial fibrillation with off-pump CABG.

## 3. Evidence from observational studies

Numerous observational studies conducted retrospectively have been published in the last few years (Table 2). Cleveland and colleagues reported one of the largest series on the clinical outcome of off-pump compared to on-pump surgery from the National Adult Cardiac Surgery Database of The Society of Thoracic Surgeons over a 2-year period [14]. With over 11,000 off-pump cases and over 100,000 on-pump cases, they reported significant reduction in operative mortality with off-pump (2.3% vs 2.9%) with an odds ratio for a reduction in the risk of death of 0.81 (95% CI: 0.70—0.91). In addition, they showed a reduction in major complications including deep sternal infection, bleeding, renal failure, and prolonged ventilation with off-pump CABG, concluding that avoidance of CPB is associated with reduced mortality and morbidity.

In a smaller series, Sergeant and colleagues reported a single-centre outcome in a series of over 3000 cases over a 6-year period [21]. They found a significant reduction in the risk of stroke in higher risk patients as well as reduced hospital stay. Differences in mortality were not significant following risk adjustment.

Experience from the UK was reported by Al-Ruzzeh and colleagues [22]. With over 5000 on-pump and 2000 off-pump cases from eight centres, they compared risk-adjusted outcomes. The findings were those of a significant reduction in the observed mortality with off-pump surgery compared to that predicted. In the on-pump group the observed mortality was similar to the predicted with an odds ratio for death with CPB of 2.3 (95% CI: 1.6—3.5). In addition, there was a reduction in all cause morbidity with off-pump proportional to risk stratification. Others have reported similar results [16,17,23].

Magee and colleagues conducted a retrospective study of 1983 off-pump CABG and 6466 ONCABG procedures from two US centres in a higher risk surgical population [15]. In this series, the mean age was 64 years, 48% had impaired left ventricular function, 30% had diabetes, and about 20% had significant comorbidity (including 5% with renal failure and 5% undergoing redo CABG). The authors used propensity score analysis and demonstrated that the off-pump group had a higher preoperative risk. Despite this, the on-pump group had higher mortality than the off-pump group with an odds ratio for CPB as a predictor of mortality at 1.9 (95% CI: 1.2—3.1). In addition, off-pump CABG was associated with a reduction in morbidity, consistent with the results of previous trials.

The major limitations of non-randomised trials are that they are inherently biased with respect to patient selection and the presumed suitability of the coronary anatomy for off-pump revascularisation. Important, however, is the fact that in most observational series the off-pump patients were higher risk when stratified according to conventional scoring systems. Risk-adjusted models and propensity matching correct for many variables but the fact is that they cannot correct for all. The latter would not include important variables such as state of the coronary targets (intramyocardial, diffuse disease, small coronaries), left ventricular hypertrophy and the surgeons' experience and technical skill. Their major value, however, is reporting 'real life' experience and do provide invaluable information that set the scene for conducting randomised controlled trials.

## 4. Randomised trials

Clinical outcomes following on-pump vs off-pump CABG have been compared in numerous prospective randomised trials (Table 3). van Dijk and colleagues carried out a multicentre trial on a cohort of 281 patients, with 139 patients randomly assigned to on-pump and 142 patients to off-pump CABG [24]. No significant differences in perioperative mortality or morbidity were demonstrated. There were no deaths and similar proportions in both groups had been free of cardiovascular events (93% and 94% with off-pump and on-pump, respectively). However, the off-pump group did show a reduction in cardiac enzyme release, duration of mechanical ventilation, and hospital stay, compared to the on-pump group.

Angelini and colleagues pooled the results of Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2),

Table 2
Outcome of mortality in observational studies comparing on-pump and off-pump surgery.

| Study | Number of patients | Mortality | | RR in mortality with OPCAB | | *p* value |
|---|---|---|---|---|---|---|
| | | OPCAB | CABG-CPB | OPCAB | CABG-CPB | |
| Cleveland et al. [14] (O/E ratio for death) | 106,423 | 11,717 | 1.02% | 0.81% | 20% | 0.001 |
| Magee et al. [15] (propensity matched) | 1,983 | 6,466 | 1.8% | 3.1% | 42% | 0.002 |
| Sabik et al. [17] (propensity matched) | 406 | 406 | 1% | 0.5% | 50% | 0.7 |
| Calafiore et al. [23] (30-day mortality (EuroSCORE >6)) | 510 | 510 | 5.9% | 3.1% | 47% | 0.04 |
| Al-Ruzzeh et al. [22] (Bayes risk based mortality) | 5,163 | 2,223 | 2.9% | 1.4% | 52% | 0.001 |
| Sharony et al. [99] (high-risk patients) | 211 | 211 | 11% | 4% | 64% | <0.05 |
| Sergeant et al. [21] (3-month mortality) | 1,593 | 1,740 | 4.1% | 3.3% | 20% | 0.2 |

Table 3
Summary of randomised controlled trials comparing on-pump and off-pump surgery.

| Study | Number of patients | | Main outcomes (off-pump vs on-pump) |
|---|---|---|---|
| | OPCAB | CABG-CPB | |
| van Dijk and colleagues [24] | 142 | 139 | Reduction in cardiac enzyme release, duration of mechanical ventilation, and hospital stay |
| Angelini and colleagues [25] | 200 | 200 | Reduced use of blood products, inotropic requirements, the rate of atrial fibrillation, chest infection, and reduced intensive care and hospital stay |
| Puskas and colleagues [27] | 100 | 100 | Reduced length of stay, transfusion requirements, and myocardial injury |
| Khan and colleagues [28] | 54 | 50 | Reduced myocardial injury and transfusion rates but inferior patency rates |
| Legare and colleagues [30] | 150 | 150 | No significant difference |
| Al-Ruzzeh and colleagues [29] | 84 | 84 | Reduction in transfusion requirements, duration of mechanical ventilation, hospital stay and neurocognitive decline. Similar graft patency |

two single-centre prospective trials, with 400 patients randomised to on-pump or off-pump CABG [25]. No significant difference in mortality was observed (0% for off-pump and 1% for on-pump). At 2 years follow-up for BHACAS 1 and over 1 year for BHACAS 2, mortality was 2% and 3%, respectively. The rate of cardiac events was 15% for off-pump compared with 18% in the on-pump group. Further benefits associated with off-pump surgery included reduced use of blood products, inotropic requirements, the rate of atrial fibrillation, chest infection, and reduced intensive care and hospital stay. The authors have recently published the long-term (6—8 years) follow-up from the same cohort reporting no difference between the off-pump and on-pump groups in graft occlusion rate (10% vs 11%), hazard of death, major adverse cardiac events and health-related quality of life [26].

Other prospective randomised trials have shown results consistent with those described above. Puskas and colleagues randomised 200 unselected patients [27]. They reported similar in-hospital and 30-day outcomes, similar completeness of revascularisation (mean of 3.39 grafts for off-pump and 3.40 for on-pump), shorter length of stay, reduced transfusion requirements, and less myocardial injury with avoidance of CPB.

Khan and colleagues randomised 104 patients to off-pump or on-pump CABG and undertook postoperative coronary angiography at 3 months postoperatively [28]. There were no deaths and the off-pump group had lower transfusion rates. However, they reported inferior patency rates in the off-pump group, stating that the learning curve for this procedure is probably substantial and may be longer than anticipated. In contrast, a randomised single-centre trial of 168 patients, Al-Ruzzeh and colleagues reported similar patency of grafts at 3-month follow-up. In addition, they reported reduction in transfusion requirements, duration of mechanical ventilation, hospital stay and neurocognitive decline with off-pump surgery [29]. Conversely, Legare and colleagues reported no significant benefits with off-pump CABG in a randomised trial of 300 patients [30]. Medium-term follow-up from the original study failed to identify any differences between the two groups in terms of all-cause mortality and cardiac events [31].

The prospective randomised trials eliminate selection bias that could not be accounted for in retrospective trials. However, the timing of randomisation is important, i.e. preoperative elimination of selection bias. However, advocates and critics of off-pump surgery have interpreted the results from these trials differently. Critics have claimed that they show little benefit with off-pump CABG, since none of the trials was able to demonstrate significant differences in more than a few selective outcome measures such as blood loss and cardiac enzyme release. The advocates, however, have emphasised that the trials were designed only to show that off-pump is at least as safe as on-pump CABG. As such, their relatively small size and use of low-risk patients meant that they were statistically underpowered to detect differences in mortality. Larger trials would therefore be required to assess any potential survival benefit especially if high-risk patients are targeted.

The inferior patency rates with off-pump CABG reported by Khan and colleagues illustrate the need to confirm intraoperative graft patency [28]. CABG is one of the few interventional vascular procedures where confirmation of a satisfactory result is not routine. Using an intraoperative fluorescent imaging system, our group reported that 2% of grafts are not patent and require revision before the conclusion of surgery and this incidence would almost certainly be higher during the learning curve for off-pump surgery [32]. It is therefore imperative and essential that graft patency is confirmed in the operating room allowing immediate revision should the need arise.

Finally, the presence of exclusion criteria for potential subjects, such as poor left-ventricular function or recent myocardial infarction, limits the applicability of any conclusions to an entire surgical population. In the OCTOPUS trial, patients were randomly allocated *after* they had been judged suitable for *either* technique, thus automatically excluding an important subset of patients. With the variety of results, it is apparent that any benefits observed might apply only to a subgroup of patients in the hands of selected surgeons.

With the increased interest in mini-extracorporeal circulation (MECC), Mazzei and colleagues randomised 300 patients into either undergoing revascularisation on CPB using a MECC circuit or with complete avoidance of CPB [33]. They reported equivalent in-hospital mortality, stroke, myocardial infarction, length of stay, and need for transfusion between groups. During 1-year follow-up, overall survival and angina-free survival were similar between groups. It must be noted, however, that the current improvements in CPB do not match the outcomes achievable by complete avoidance of CPB as the CPB circuit will always require aortic cannulation and cross-clamping to achieve global myocardial arrest whereas off-pump provides the opportunity for complete avoidance of aortic manipulation especially in elderly patients with severe aortic atherosclerosis. In addition, MECC carries the risk of air embolism associated with the use of a closed venous reservoir if air is accidentally entrained in the venous line.

## 5. Systematic review

### 5.1. Inflammatory response

Cardiopulmonary bypass is associated with a systemic inflammatory response syndrome (SIRS). Contact of blood components with the artificial surfaces of the bypass circuit, ischaemic cardiac arrest and reperfusion injury is considered the main causes of this inflammatory response [34,35]. Humoral and cellular responses involving complement, coagulation, fibrinolytic and kallikrein cascades, neutrophils, platelets and endothelial cells contribute to SIRS. The latter is characterised by increased capillary permeability, interstitial fluid accumulation and malperfusion at the capillary/end-organ level [36]. In its most extreme form this may lead to end-organ dysfunction, typified by coagulation abnormalities and cerebral, renal, myocardial and respiratory morbidity [35]. It would logically follow that avoidance of CPB would result in a significant attenuation of this inflammatory response and this has been substantiated by several studies.

A study by Wan and colleagues [37] of 44 consecutive patients who had on- or off-pump operations found that the release of interleukin (IL)-8 and IL-10 was significantly lower in the off-pump group. Matata and colleagues [38] showed a significant increase of lipid hydroperoxides, protein carbonyls, and nitrotyrosine (markers of oxidative stress) in the on-pump group but not in the off-pump group. C3a and elastase levels increased rapidly upon institution of CPB, and this was followed by increases in IL-8, TNF-$\alpha$, and E-selectin, whereas the increase in these markers was minimal in the off-pump group [38]. Other studies have measured the inflammatory response associated with off-pump vs conventional CABG and demonstrated a reduction in the degree of activation of inflammatory markers, including IL-6, IL-8, tumour necrosis factor (TNF)-$\alpha$, C3a and C5a [39] and PMN elastase [40].

### 5.2. Myocardial injury

Myocardial injury as assessed using cardiac enzyme release has been demonstrated following cardiac surgery. This results from ischaemic arrest during on-pump surgery, but also following temporary coronary occlusion/snaring during off-pump surgery. Findings of a reduction in myocardial injury have been demonstrated in several studies with a reduction in the release of troponin and CK-MB [24,28,30]. In a randomised single-centre trial of 60 patients, our group reported significantly higher troponin I in patients undergoing on-pump surgery; the latter associated with significantly worse postoperative LV function as assessed using cine MRI [41]. In another randomised trial using cardiac magnetic resonance imaging to assess right ventricular function postoperatively, significant impairment in the right ventricular stroke volume index was identified that did not differ between the on-pump and the off-pump groups [42].

### 5.3. Cerebral injury

Neurological morbidity following cardiac surgery is the most significant and disabling complication of CABG. Although cerebral injury also occurs after major non-cardiac surgical procedures [43], it is more common and severe after operations using CPB, supporting the potentially deleterious effects of extracorporeal circulation [44]. Cerebral injury describes a range of disorders that can be broadly classified, in decreasing order of severity but increasing incidence, as stroke, delirium (encephalopathy) and neurocognitive dysfunction. Several risk factors are associated with neurological injury including advancing age, diabetes, severe atherosclerotic disease and previous history of neurological disease [45]. The aetiology of postoperative cerebral injury is complex and multifactorial. The main pathophysiological mechanisms include the systemic inflammatory response syndrome, cerebral embolisation and hypoperfusion. Of all the pathophysiological mechanisms related to CPB, intraoperative cerebral microembolisation is probably the most important [46—48].

Several large observational studies have reported favourable neurological outcome with off-pump surgery. In the report from the Society of Thoracic Surgeons (STS) Database, comparing on-pump and off-pump patients, the hazard ratio for stroke with the latter was 0.6 [14]. In a study of almost 68,000 patients Racz and colleagues reported a reduction in the rate of perioperative stroke from 2% in the on-pump group to 1.6% in the off-pump group [49]. Likewise, in an analysis of over 17,000 patients Mack's group reported a reduction in stroke from 2.1% in on-pump to 1.4% in the off-pump group [50]. Moreover, in a meta-analysis by Sedrakyan and colleagues, there was an apparent 50% reduction in the relative risk of stroke with off-pump CABG [51].

Other studies have highlighted the importance of avoiding or minimising intraoperative manipulation of the aorta in addition to the avoidance of CPB. In a study by Calafiore, patients were divided into two groups: the first group underwent conventional CABG using CPB with or without aortic side-clamping, and the second underwent off-pump CABG with or without aortic side-clamping. The rate of postoperative stroke in the on-pump group with and without aortic side-clamping was 2.3% and 1.2%, respectively [52]. In the off-pump group, the rate of stroke was 0.2% in the group without any aortic manipulation compared to 1.1% in those where a side-clamp was used. Therefore, the best results were achieved with avoidance of CPB combined with minimal aortic manipulation. Likewise, Lev-Ran and colleagues reported a marked reduction in the rate of stroke and mortality with avoidance of aortic manipulation in a study of 160 consecutive off-pump CABG patients over 75 years of age [53].

The largest study of delirium in off-pump surgery has recently been conducted by the Leipzig group. They described a cohort of 16,000 cardiac surgical patients undergoing CABG with and without CPB as well as open cardiac procedures over a 5-year period [54]. The incidence of delirium was 8% in patients undergoing conventional CABG with CPB compared to 2% with off-pump surgery. This study identified numerous pre- and intraoperative predictors of postoperative delirium including cerebrovascular disease, peripheral vascular disease, atrial fibrillation, diabetes mellitus, impaired left ventricular function, urgent operation, intraoperative haemofiltration, prolonged operation and high transfusion requirements. Furthermore, off-pump surgery and younger patient age conferred a protective effect against postoperative delirium. While this was not a randomised trial, it provides incremental evidence of the potential neuroprotective effects of off-pump surgery.

The evidence that off-pump CABG reduces cognitive dysfunction is conflicting with reports of marked [29,55], modest [56] or no benefits [57]. In the first prospective trial assessing cognitive dysfunction following on-pump and off-pump surgery, similar rates of cognitive decline were reported in both groups [58]. Similar observations were noted in a randomised trial by Van Dijk and colleagues where cognitive decline occurred in 21% in the off-pump group and 29% in the on-pump group (relative risk [RR], 0.65; 95% confidence interval [CI], 0.36–1.16; $p = 0.15$) [56]. The limitations of these studies include the small sample size, rendering them underpowered to detect a statistical difference, and the use of a young low-risk population who are at least at risk of such deficits. Failure to consistently demonstrate significant improvement in cognitive dysfunction with off-pump surgery may be due to the high signal-to-noise ratio associated with neuropsychological testing and which may hide subtle but real differences [59].

In contrast, the study by Zamvar and colleagues reported a marked reduction in postoperative cognitive dysfunction (defined as deterioration in score of one standard deviation in two or more tests) with off-pump surgery (27% vs 63%, $p < 0.01$) [55]. The fact that the latter study included well-matched groups receiving the same number of grafts, as well as having complete early and late follow-up may partly explain the discrepancy with the results from other trials. More recently, in a randomised trial, Amrani's group reported better neurocognitive function with off-pump compared to on-pump surgery at six weeks and six months postoperatively [29]. Our group has reported significant reduction in frontal cerebral activity early after on-pump surgery but not after off-pump surgery as detected using functional magnetic resonance imaging [60].

As microembolisation can be minimised with complete avoidance of aortic manipulation, total arterial revascularisation using composite grafts has the potential of significantly reducing the incidence of neurocognitive injury. Several reports have shown a significant reduction in microembolisation with avoidance of CPB [61–63]. Work from our own group demonstrated a significant reduction in the proportion of solid microemboli, thought to be most harmful, in the off-pump group from 22% to 12% [63]. Recent work from Hammon and colleagues reported a significant reduction in the incidence of cognitive deficits at six months following coronary artery bypass grafting with minimal aortic manipulation [64]. Therefore, it seems reasonable to assume that off-pump surgery confers significant neuroprotection compared to on-pump surgery especially in higher risk groups and more specifically in those with significant aortic atherosclerosis.

### *5.4. Renal injury*

Acute renal failure remains a frequent and serious complication of cardiac surgery. Its incidence varies depending on definition and affects 1–5% of all patients [65–67]. While it may be often regarded as a transient injury that recovers with conservative management in most patients, such complacency is strongly dismissed by the evidence supporting a significant increase in mortality and morbidity that accompanies perioperative renal dysfunction [65–67]. Severe acute renal failure (ARF) requiring dialysis after cardiac surgery is an independent risk factor for death [68]. In a multi-centre observational study from the Veterans Affairs health system, Chertow and colleagues analysed a large cohort that included 42,773 patients. After adjusting for the preoperative risk factors as well as other postoperative morbidities that may influence mortality, the odds ratio for mortality associated with ARF requiring dialysis was 7.9 [68]. In addition, even mild preoperative renal dysfunction represents an independent predictor of in-hospital mortality, morbidity, mid-term and long-term survival [69–71]. Postoperative renal impairment is also associated with prolonged hospital stay and increased cost.

The pathophysiology of renal injury is multifactorial and is related to perioperative renal hypoperfusion and the presence of endogenous and exogenous nephrotoxins and microembolisation [13–15,27,72–78]. As most of the pathophysiological mechanisms resulting in postoperative renal injury are related to the use of CPB, it follows that a theoretical reduction in the incidence and severity of renal impairment may be achieved with elimination of extracorporeal circulation especially in high-risk patients [79,80]. However, the current evidence for off-pump surgery in reducing postoperative renal injury is conflicting.

A randomised study by Ascione and colleagues [72] demonstrated a significant renoprotective effect of off-pump surgery, whereas Tang and colleagues demonstrated no significant differences despite a trend of less injury in the off-pump group [81]. In a small observational study, Loef and colleagues demonstrated a significant reduction in transient renal injury with off-pump CABG [77]. We similarly reported that avoidance of cardiopulmonary bypass may reduce renal injury particularly in higher risk patients [76]. The above studies, however, only included relatively low-risk patients and it has been argued that the benefits of off-pump surgery may only be evident in those at higher perioperative risk.

In a propensity-based study of over 2000 patients, Weerasinghe and colleagues reported the potential for off-pump surgery in reducing the risk for minor and major renal adverse outcomes after coronary artery bypass grafting [82]. As regards the conduct of CPB, Tang and colleagues showed that leukodepletion may offer some renal protection in low-risk patients during CABG [81]. Additionally, a large observational trial demonstrated that renal outcomes may be improved if the nadir haematocrit concentration during cardiopulmonary bypass is kept within the identified optimal range of 21–25% [83]. As regards the flow characteristics during extracorporeal circulation, Kocakulak and colleagues reported superior renal protection with pulsatile flow in high-risk patients [84].

A prospective randomised comparison of 200 unselected patients undergoing off-pump vs conventional CABG reported no difference in the postoperative incidence of renal failure between the two groups [27]. Several large observational studies that included high-risk patients have reported a significant reduction in the frequency of renal failure in patients undergoing off-pump CABG [14,15,73,74,85]. This is consistent with results from the meta-analysis by Reston and colleagues [13].

Di Mauro studied renal outcomes in over 2600 patients undergoing CABG. Of those, 160 patients had preoperative renal impairment. Acute renal failure occurred in 2.9% of the off-pump patients and 7.9% of those undergoing conventional CABG ($p < 0.001$). In the group with abnormal renal function, no significant differences were demonstrated between on-pump and off-pump (16% vs 13%, $p = 0.5$).

### 5.5. Atrial fibrillation

AF remains one of the most common complications following CABG and affects 20–40% of patients. Ascione reported a significant reduction in the rate of AF in a randomised controlled trial of 200 patients (39% with on-pump vs 8% with off-pump). In a meta-analysis by Athanasiou and colleagues, there was a significant reduction in post-operative atrial fibrillation in elderly patients undergoing off-pump surgery compared to those having surgery with CPB [86].

### 5.6. Graft patency and adequacy of revascularisation

The quality of anastomosis and adequacy of revascularisation has been a major criticism of off-pump surgery with some demonstrating inferior [10,28,87] or comparable graft patency rates [29,88,89]. As outlined earlier, a randomised trial by Khan and colleagues reported inferior patency rates with off-pump CABG (88% vs 98%) [28]. This may however be explained by the fact that both surgeons in the trial were early in their off-pump experience and performed only 13% of their workload off-pump. Four randomised controlled trials have reported equivalent patency rates with on-pump and off-pump CABG [29,89–91]. In addition to the trial by Khan and colleagues, two meta-analyses have reported inferior patency rates with off-pump CABG [10,87]. Our group reported no significant differences in graft patency rates between on-pump and off-pump as assessed using an intraoperative fluorescence imaging system [32]. Puskas and colleagues reported a patency rate of 93.6% with off-pump compared to 95.8% with conventional revascularisation at 1-year follow-up. The difference was, however, not statistically significant [89].

Using the New York database over a 3-year period, Hannan and colleagues reported freedom from revascularisation of 89.9% with off-pump vs 93.6% with on-pump surgery ($p < 0.0001$) [92]. In addition, off-pump surgery was associated with lower in-hospital mortality and risk of stroke. What was not certain was if this represented fewer grafts in the off-pump group or a higher incidence of graft failure.

Kobayashi and colleagues demonstrated similar completeness of revascularisation and early graft patency in a randomised trial of around 170 patients (Japanese off-pump coronary revascularisation investigation) [90]. Similarly, Lingaas and colleagues conducted a randomised trial of 120 patients with angiographic follow-up at 1 month and 12 months. Off-pump coronary bypass surgery provided the same angiographic graft patency as the on-pump technique [91]. In the most recently published meta-analysis, Moller and colleagues reported no increase in renewed coronary revascularisation with off-pump surgery, but this may be due to the relatively small sample size.

This issue remains an important concern with off-pump surgery and there is conflicting evidence as to whether the latter is associated with worse graft patency. Part of this may be explained by careful patient selection and the skills and experience of the operating surgeon. However, there may also be a genuine increase in graft failure rate with off-pump surgery due to eliminating the antiplatelet effects of CPB. While there was a higher risk of graft failure reported by Khan and colleagues [28], this was not observed by Puskas and colleagues [89] or Angelini and colleagues [26].

### 5.7. Economic consideration

Economics of a surgical procedure remains a very important element in healthcare. Cost saving with off-pump has been demonstrated by several randomised controlled trials. In the BHACAS trial, there was a 25% cost saving per patient [25]. Nathoe and colleagues reported a saving of $1800 per procedure [93] and Puskas and colleagues demonstrated a saving of $2272 at hospital discharge and $1955 at 1 year postoperatively [89].

### 5.8. Training

Training junior surgeons in a novel surgical strategy with a prominent learning curve is a challenge and requires dedication and modification of training methods to ensure acquisition of the appropriate skills. The feasibility and safety of training in off-pump surgery has been reported [94–97]. The Bristol group also demonstrated the safety of trainees operating on high-risk patients without CPB [98].

## 6. Summary

In summary, the randomised controlled trials to date have been conducted in relatively low-risk patients who are at least risk of the deleterious effects of CPB. Consequently, they may not reflect overall practice that will include many higher risk patients. Despite that, they demonstrated that off-pump CABG is at least as safe as on-pump surgery with additional benefits such as the reduction in myocardial and cerebral injury, rate of transfusion, cost and the length of hospital stay. Several large databases reflecting the 'real world' experience reported a reduction in mortality and morbidity with the highest gains realised in those at most risk. The most important cause for potential concern has been ensuring complete revascularisation and long-term graft patency with off-pump surgery. It must also be noted that off-pump surgery is more technically demanding compared to operating on the arrested heart using CPB. Enthusiasts of the off-pump technique report equivalent revascularisation rates and graft patency, but evidence in the literature is conflicting. It is self-evident, however that completeness of revascularisation should not be compromised for the sake of avoiding cardiopulmonary bypass in patients at low-to-medium risk. The full benefits of off-pump surgery may however be in those elderly, high-risk patients with significant aortic atherosclerosis where the risk of stroke is prohibitively high. In this group of patients, avoidance of CPB and aortic manipulation by performing composite arterial grafts may significantly improve outcome. It can be argued, however, that these are the very cases where the techniques of off-pump revascularisation should already have been perfected as these patients are least suitable for learning the technique. The results of off-pump surgery are therefore dependent on a complex interaction of many factors that include the skill and experience of the surgeon and appropriate patient selection for certain techniques. It is therefore reasonable to conclude that off-pump surgery is a very safe and efficacious alternative to conventional revascularisation in certain hands and should be increasingly utilised in the high-risk groups especially those at high risk of postoperative stroke from aortic atherosclerosis. In low-risk patients, however, CPB remains safe and completeness of revascularisation should not be compromised. To this end, both methods of revascularisation will continue to have a role in revascularisation and they both continue to evolve. Further trials will continue to supplement the current knowledge we have on the subject with the aim of making coronary surgery even safer than it is today.

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