Impact of Off-pump and On-pump Coronary Artery Bypass Grafting on In-hospital Mortality and Mid-term Survival of Octogenarians

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June 2, 2021

Abstract

Background: Octogenarians are being increasingly referred for coronary artery bypass grafting (CABG). However, there is a paucity of studies reporting impact of choice of surgical revascularization strategy on in-hospital mortality and mid-term survival of octogenarians. We evaluated our institutional experience to determine the impact of off-pump and on-pump CABG on in-hospital mortality and mid-term survival of octogenarians. Methods: We retrospectively analysed prospectively collected data from the Patients Analysis and Tracking System database (Dendrite Clinical Systems, Oxford, UK) for all isolated first-time CABG procedures with at least 2 grafts performed at our institution from January 2000 to September 2017. Over the study period, 566 octogenarians underwent either off-pump (N = 374) or on-pump CABG (N = 192). Short-term outcomes including in-hospital mortality as well as mid-term survival was compared for the two groups. Results: The two groups had similar preoperative demographics and mean number of distal anastomoses (off-pump: 2.7 ± 0.6 [median 3] vs on-pump: 2.7 ± 0.3 [median 3]; P=0.6). However, more bilateral internal mammary artery grafts were performed in the off-pump cohort compared to on-pump cohort (117 [31.3%] vs 22 [11.5%]; P <0.001). In-hospital mortality for the entire cohort was 5.7% with significantly fewer deaths in the off-pump cohort (4.3% vs 8.3%; P=0.04). The remaining in-hospital outcomes were similar. Kaplan-Meier survival at 1 year (89.7% vs 82.9%; P=0.048) and 5 year (71.1% vs 61.3%; P=0.038) was significantly better for the off-pump cohort. Conclusion: Octogenarians experience lower in-hospital mortality and improved mid-term survival after off-pump CABG compared to on-pump CABG.

Introduction

Despite the resurgence of off-pump coronary artery bypass surgery nearly 30 years ago, its role and indications remain unclear. This is even after the publication of 115 randomised controlled trials (RCTs) and over 60 meta-analyses comparing on- and off-pump surgery.[1] The detractors of off-pump coronary artery bypass grafting (CABG) cite worse graft patency, higher 1-year and late cardiac mortality.[2] Analyses of various RCTs raise concerns about the completeness and effectiveness of revascularisation.[3] This is due to under grafting of the lateral and inferior wall targets.[4] Additionally, distal and poorly constructed anastomoses account for increased incidence of recurrent angina, higher rate of re-intervention and worse long-term outcomes.[5]

Trials that have sought to include only experienced surgeons have addressed these concerns and report equivalent outcomes up to five years for both techniques.[6] There are data to reflect surgeon and unit volume affecting outcomes in off-pump surgery.[7] The UK National Adult Cardiac Surgery Audit Database demonstrated that off-pump surgery performed by surgeons with a preference for the technique had superior outcomes when compared to on-pump surgery performed by surgeons with a preference for it.[8]

Additional analyses of RCTs have demonstrated that there are certain subpopulations nested within the cohorts that might benefit from the off-pump approach.[9] These include patients who are high-risk and

the benefits for them are mostly recognised in the perioperative period.[9] Most evidence suggests that off-pump surgery is associated with reduced incidence of peri-operative stroke, renal failure, blood transfusion, respiratory failure, atrial fibrillation, wound infection and length of stay.[10]This is even more important in a growing subpopulation that is being increasingly referred for surgery, namely octogenarian patients.[11] It is known that increased age and associated frailty are independent factors for adverse outcomes after cardiac surgery and are considered as such in all risk assessment models.[11]

In this study we sought to determine outcomes in our octogenarian population undergoing off-pump vs on-pump surgery undertaken by high volume surgeons at an experienced unit. Our primary outcome measures were in-hospital mortality and mid-term survival at -1 and -5 years respectively. We also evaluated post-operative complications and any inherent differences in between the groups that would explain the outcomes.

Methods

We retrospectively analysed prospectively collected data from the Patients Analysis and Tracking System database (Dendrite Clinical Systems, Oxford, UK) for all isolated first-time CABG procedures with at least 2 grafts performed at our institution from January 2000 to September 2017.

We have previously published our detailed methodology for patient selection.[7] Briefly, the patient admission and tracking system (PATS database; Dendrite Clinical Systems, Oxford, UK) captures detailed information on a wide range of pre, intra, and post-operative variables (including complications and mortality) for all patients undergoing cardiac surgery at our institution. Reproducible cleaning algorithms were applied to the database, which are regularly updated as required. Duplicate records were removed, transcriptional discrepancies were harmonized, and clinical conflicts and extreme values were corrected or removed. The data are validated and also submitted to the National Institute for Cardiovascular Outcomes Research (National Adult Cardiac Surgery Audit registry) annually. The study was conducted in accordance with the principles of the Declaration of Helsinki. The local audit committee approved the study, and the requirement for individual patient consent was waived due to the retrospective nature of the study.

Study population

Over the study period, a total of 10870 patients were identified, off these 566 were octogenarians. These were split into 374 off-pump CABG and 192 on-pump CABG, performed by surgeons with exclusive off-pump and on-pump practices, respectively. The operative approach for revascularisation utilised by the surgeon did not influence referral pattern and all surgeons operated on a similar case mix. Indications for surgical intervention were determined at a weekly multidisciplinary review meeting which involved imaging cardiologists, interventional cardiologists, cardiac surgeons and advanced nurse practitioners. The patients were placed on a specific waiting list according to the urgency of their procedure.

Operative techniques

We have previously published our operative technique in detail.[11] Median sternotomy approach was used for all multivessel CABG. The choice of conduits was based on surgeon's preference, patient characteristics and anatomy. All patients had 2 or more grafts utilising combination of internal mammary, radial arteries and/or long saphenous vein grafts. The left and the right internal mammary artery were harvested with minimal trauma as pedicled or skeletonized grafts, based on the surgeon's preference, and treated with papaverine solution before use. The radial artery was harvested from the non-dominant upper limb after assessing adequacy of collateral circulation using modified Allen's test. The great saphenous vein as well as the radial artery were harvested using open or endoscopic technique.

Conventional CABG on cardiopulmonary bypass (CPB) was performed at 34° C. Single two-stage right atrial cannulation and an ascending aorta perfusion cannula were used for instituting CPB. Standard bypass management included membrane oxygenators, arterial line filters, and nonpulsatile flow of 2.4 L/min/m^2, with a mean arterial pressure of greater than 50 mmHg. The myocardium was protected by using intermittent antegrade cold blood cardioplegia (blood-crystalloid ratio, 4:1). Anticoagulation was achieved using 300 U/kg of heparin. If required, heparin was supplemented to maintain the activated clotting time of more than 480

seconds and was reversed by protamine at the end of the procedure. All distal and proximal anastomoses on CPB were performed during a period of single aortic cross-clamping.

For off-pump CABG, the heart was stabilized using suction-irrigation tissue stabilization system. A deep pericardial retraction suture helped position the heart for grafting. Anticoagulation was achieved with 150 U/kg of heparin. If required, heparin was supplemented to maintain the activated clotting time of more than 300 seconds and was reversed by protamine at the end of the procedure. Blood pressure was continually optimized during the procedure, and the mean arterial pressure was maintained higher than 60 mmHg by repositioning the heart and by intravenous fluids or selective use of vasoconstrictors or both. Proximal graft anastomoses to the aorta were performed with partial cross-clamping of the ascending aorta. Each distal anastomosis was followed by construction of the corresponding proximal anastomosis.

Postoperative management

Postoperative intensive care unit management was standardized for all patients. All patients received intravenous nitroglycerin (0.1-8 μg/kg/min) infusions for the first 24 hours unless hypotensive (systolic blood pressure < 90 mm Hg). Choice of inotropic agents was dictated by the hemodynamic data. Other routine medications included daily aspirin and resumption of cholesterol-lowering agents and beta blockers unless contraindicated. Diuretics, angiotensin-converting enzyme inhibitors, other anti-hypertensive agents and oral anticoagulants were gradually introduced when indicated clinically. Dual anti-platelet treatment for 1-year post-operatively became the standard of care in our institution from 2015 onwards for all CABG patients unless contraindicated.

Variables

Demographic and pre-operative variables included age, gender, previous myocardial infarction, diabetes, hypercholesterolaemia, hypertension, renal disease (preoperative serum creatinine of [?]200 μM/l), respiratory disease, cerebrovascular disease, peripheral arterial disease, atrial fibrillation, presence of three disease, left main disease, pre-operative left ventricular function (good >50%; fair 30–50%; poor <30%) and urgency of the procedure (operation performed <24 h vs >24 h from time of referral).

Intraoperative variables included types of grafts used, grafts per patient, CPB time, aortic cross-clamp time, conversion and index of completeness of revascularization (ICOR). The ICOR was defined as the total number of distal grafts constructed divided by the number of the affected coronary vessels reported on the preoperative coronary angiogram. Complete revascularization was assumed when the ICOR was 1 or greater.

Post-operative variables used were reoperation for bleeding, myocardial infarction (MI) during index hospitalization, pulmonary complications defined as (prolonged ventilation of longer than 24 h, chest infection, pleural effusion), sternal wound complications, neurological complications (stroke or transient ischaemic attack), need for haemofiltration or dialysis, reintubation and/or tracheostomy, gastrointestinal complications and mortality at 30-days. The long-term outcomes of interest were all-cause mortality beyond 30-days out to -5years. Information about death was obtained from the institutional database and the National General Register Office for all patients. Data regarding postoperative complications and survival were available for all patients in the study.

Statistical analysis

All continuous variables were tested for normality using the Kolmogorov–Smirnov test. Data are presented as percentages, mean ± standard deviation (SD), or median (interquartile range). Differences in proportions were tested with Chi-square test or Fisher exact test, and differences in continuous variables were tested with independent t-test or Wilcoxon signed-rank sum test for parametric and nonparametric variables, respectively. The Kaplan Meier estimate was used to calculate survival. The log-rank test was used to assess for the presence of significant differences in survival. A p-value<0.05 was considered significant. Data were analyzed using SPSS version 26.

Results

Demographics and pre-operative characteristics

The two groups had similar demographics and pre-operative characteristics (Table 1). The mean age was 82.3±2.3 in off-pump vs 82.1±1.9 in the on-pump group, P = 0.331. There were no statistically significant differences for gender, co-morbidities, presence of three vessel disease (259 [69.3%] vs 139 [72.4%]; P = 0.782), left main stem involvement (133 [35.6%] vs 67 [34.9%]; P = 0.794) or poor ventricular function (20 [5.3%] vs 8 [4.2%]; P = 0.351). Similar proportion of cases were carried out as elective case mix in both groups (210 [56.1%] vs 102 [53.1%]; P = 0.218).

Outcomes

The conversion rate in our series was 1 case (0.3%) for the off-pump cohort. The mean number of distal anastomoses (off-pump: 2.7 ± 0.6 [median 3] vs on-pump: 2.7 ± 0.3 [median 3]; P = 0.6) (Table 2). However, more bilateral internal mammary artery grafts were performed in the off-pump cohort compared to on-pump cohort (117 [31.3%] vs 22 [11.5%]; P < 0.001). There was an increased number of multiple arterial grafts for the off-pump cohort (174 [46.5%] vs 43 [22.4%]; P = 0.04). This included increased number of sequential grafts (91 [24.3%] vs 12 [6.3%]; P < 0.001) and Y grafts (141 [37.7%] vs 18 [9.4%]; P< 0.001). There was increased arterial grafting performed to the right coronary artery territory (58 [15.5%] vs 18 [9.4%]; P = 0.05). The preferred second arterial conduit was the right internal mammary artery with the third arterial conduit as the radial artery.

Complications

There were no differences in re-operation for bleeding/tamponade (6 [1.6%] vs 6 [3.1%], P = 0.07, or other complications listed in Table 3. There was a reduction in peri-operative stroke in favour of the off-pump group 8 (2.1%) vs 11 (5.7%), however this did not reach statistical significance (P = 0.06). There were significant reductions in renal complications (post-operative hemofiltration and dialysis) in favour of off-pump cohort 18 (4.8%) vs 16 (8.3%), P = 0.05 and 30-day mortality (16 [4.1%] vs 16 [8.3%], P = 0.04).

Survival

Kaplan-Meier survival at 1 year (89.7% vs 82.9%; $P_{\text{log-rank}}$ 0.038) and 5 year (71.1% vs 61.3%; $P_{\text{log-rank}}$ 0.038) was significantly better for the off-pump cohort (Figure 1).

Discussion

In the current study we report improved mid-term survival in a large cohort of octogenarians with multivessel disease when revascularized with off-pump versus on-pump surgery. Off-pump surgery was associated with lower incidence of post-postoperative renal complications and trend towards lower neurological complications with no difference in other complications when compared to on-pump group. The 30-day mortality was lower with the survival benefit maintained in-favour of off-pump out to 1- and 5-years. These results are in keeping with recent reviews of retrospective series and meta-analyses in octogenarian populations.[12]

These results are pertinent as octogenarians are the fastest growing population group in economically developed countries and the percentage of patients in this cohort with coronary disease is expected to increase. The early benefits of reducing renal and neurological complications in favour of off-pump group might be due to avoiding the deleterious effects of CPB.[13] On-pump surgery elicits a complex prothrombotic and pro-inflammatory response that peaks within the time frame of end of CPB to the early hours.[13]Certain cellular and molecular changes persist for weeks after surgery and lead to systemic inflammatory reaction, platelet and coagulation activation, oxidative free radical generation, endothelial dysfunction and sequelae of non-pulsatile flow.[14] Some of these changes also occur in the off-pump group but are more pronounced following CPB. Additionally, the efficacy of anti-platelets might be reduced in the on-pump cohort of patients in the initial post-operative phase as there is increased platelet turnover.[15] Some authors note that these effects might persist up to 3 months post-operatively with increased production of thromboxane A2, increases in immature platelets, total platelets, platelet mass, thrombopoietin, IL-6, glycocalicin, leukocytes, and high-sensitivity CRP.[14,15] This could lead to initial graft thrombosis and failure especially in vein grafts.

Octogenarians undergoing CABG represent a high-risk group as they have advanced atherosclerotic disease, low grade ongoing systemic inflammation and multiple co-morbidities. These along with myocardial ischaemia due to cross clamping, reperfusion injury, plaque rupture, microembolization and platelet aggregation might increase the risk of neurological and renal complications in the on-pump cohort.[1, 16]

The reno-protective effect of off-pump surgery has been previously reported. Meta-analysis of nine observational studies and one RCT (1,850 on-pump CABG; 1,183 off-pump CABG) that included non-dialysis dependent renal dysfunction patients undergoing CABG found that off-pump CABG was beneficial in preventing acute renal failure (OR 0.55; P=0.01) and early mortality was lower following off-pump CABG (OR 0.62; P=0.04).[17] Another study from the STS database (742,909 patients (584,348 on-pump CABG; 158,561 off-pump CABG) looking at patients undergoing non-emergent isolated CABG according to preoperative renal function (looking at estimated glomerular filtration rate [GFR]) evaluated the effect of the use of CPB during CABG on in-hospital mortality and incident renal replacement therapy. A propensity matched analysis showed that off-pump surgery was associated with a reduced rate of in-hospital mortality and renal replacement therapy. The risk reduction became more pronounced with decrease in preoperative renal function ranging from 0.05 per 100 patients for eGFR >90 mL/min per 1.73 sq. m to 3.66 per 100 patients for eGFR of 15–29 mL/min per 1.73 sq. m.[18] Additional data from the nephrology literature similarly explains the reno-protective effects in off pump surgery with reduced haemodilution, less thrombotic and inflammatory oxidative stress to the nephron, maintenance of pulsatile renal flow and perfusion pressure to the kidney.

Another factor which could explain the positive impact of off-pump CABG in terms of reduced mortality and improved mid-term survival is that high risk patients such as those above 80 are most frequently excluded in RCTs. It is exactly these patients who are most likely to benefit from off-pump surgery. Data from meta-analysis of 100 RCTs showed outcomes in favour of off-pump CABG for post-operative MI (P<0.01), all-cause mortality (P<0.01) and cerebral stroke (P<0.01).[9] Data from the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) Registry by using propensity score-adjusted logistic regression or Cox proportional hazard models based on pre-operative morbidities showed the composite outcome in favour of off pump surgery when analysing death, MI and stroke at OR 2.7 (P=0.03) in the intermediate risk and OR 2.6 (P=0.01) in the high-risk tertile.[19]

The most plausible explanation for improved 1-year and 5-year survival could be that our off-pump cohort had same number of grafts as the on-pump group and there was increased utilisation of arterial grafting including bilateral mammary artery grafting, multiple arterial grafting, radial artery use and increased arterial grafts to the RCA territory. The enhanced use of arterial grafts during off-pump revascularization could have improved midterm survival.

The effect of total arterial grafting in the Arterial Revascularisation Trial (ART) was analysed out to 10 years according to the graft received (as treated principle). The final population had 1084 patients of whom 390 had single arterial graft and remainder had multiple arterial or total arterial grafts. There was a significant trend towards reduction of 10-year mortality in the multiple arterial and total arterial group (P = 0.02). The total arterial group had the lowest mortality (HR 0.68, 95%CI 0.48-0.96; P = 0.03) and a significant risk reduction of composite end point of death, MI, stroke and repeat revascularisation (HR 0.71, 95%CI 0.53-0.94; P = 0.02).[20]

The initial divergence of Kaplan Meier survival curves in our study population could be due to the benefit of avoiding cardiopulmonary bypass in the immediate post-operative setting with reduced renal complication rates and morbidity as well as mortality. The continued improved survival advantage in the off-pump cohort could be the result of increased arterial grafting to lateral wall and right sided vessels.

Limitations

This is a single centre retrospective study which is observational in nature. Hence, there may be unidentified variables affecting outcomes that remain unaccounted for in the final analysis. Additionally, the study spans nearly 17 years with several improvements in operative techniques as well as anaesthetic and postoperative

management during this period that could have influenced the outcomes.

Our institution is a high-volume facility with dedicated off-pump surgical teams and a focus on continuous improvement in pre-operative work-up, peri-operative care, intra-operative anaesthetic and surgical expertise and standardised post-operative management algorithms. The results thus might not be generalizable to other units and their respective settings.

Finally, we report on the clinical outcome measures and survival of the patients. We have not performed angiographic graft surveillance of the patients and do not report longitudinal data on graft patency.

Conclusions

Surgical revascularisation leads to favourable outcomes in octogenarian population where both off- and on-pump strategies are safe and effective. Lowered in-hospital mortality with off-pump CABG could be explained based on avoidance of inherent risks of CPB and cardioplegic arrest including haemodilution, non-pulsatile arterial flow, global myocardial ischemia, atherosclerotic embolization from aortic manipulation, and systemic inflammatory response. Improved mid-term survival with off-pump CABG could be explained based on increased bilateral internal mammary artery usage and multiple arterial grafting in the off-pump cohort. The decision to offer one or the other treatment preferentially must be guided by local expertise in the surgical revascularisation team set-up.

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Conflicts of interests: None

Funding: None

Authorship statement: All authors confirm that they substantially contributed to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

Drafting the work or revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Figure Legend

Figure 1. Comparison of Kaplan-Meier survival for off-pump and on-pump cohorts

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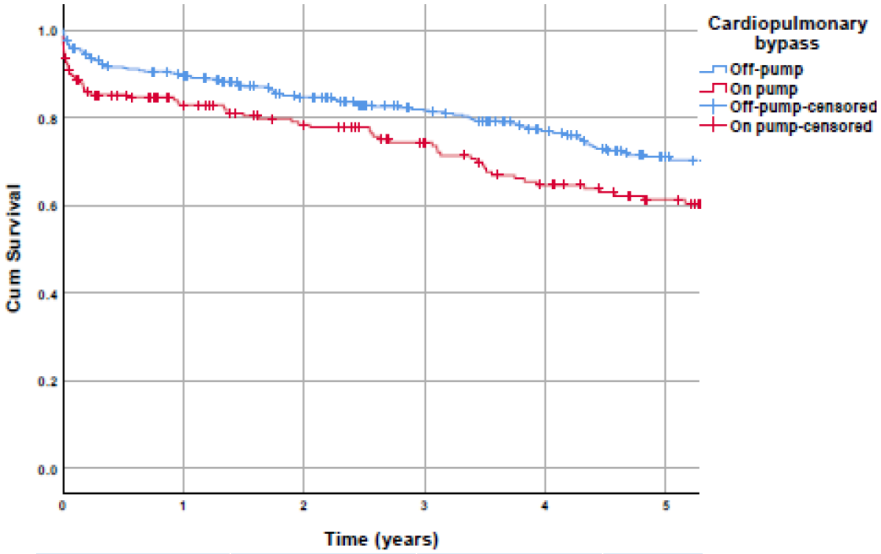

Groups	Off pump (N=374) (%)	On pump (N=192) (%)	P value
30 – day mortality	16 (4.3)	16 (8.3)	0.048
1-y KM estimated survival	89.7%	82.9%	0.038
5-y KM estimated survival	71.1%	61.3%	