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Original Research Article

Comparative Evaluation of Off-Pump versus On-Pump Coronary Artery Bypass Grafting on Early Postoperative Inflammatory Markers and 30-Day Mortality: A Prospective Cohort Study

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Abstract

Background: Coronary artery bypass grafting (CABG) remains the cornerstone revascularization strategy for multivessel coronary artery disease. Cardiopulmonary bypass (CPB) utilized during on-pump CABG (ONCAB) is known to provoke a systemic inflammatory response that may adversely influence postoperative outcomes. Off-pump CABG (OPCAB) avoids CPB, theoretically mitigating this inflammatory cascade, yet the comparative clinical significance of attenuated inflammation on hard clinical endpoints remains contested.

Methods: A prospective cohort study was conducted at cardiac surgery center. A total of 342 consecutive patients undergoing isolated primary CABG were enrolled: 168 in the OPCAB group and 174 in the ONCAB group. Inflammatory markers were measured preoperatively and at 6, 24, and 72 hours postoperatively. Primary outcomes included peak postoperative inflammatory marker concentrations and 30-day mortality.

Results: Peak CRP levels were significantly lower in the OPCAB group (98.4 ± 32.7 vs. 142.6 ± 41.3 mg/L; $p < 0.001$). Similarly, peak IL-6 (186.3 ± 72.4 vs. 298.7 ± 94.8 pg/mL; $p < 0.001$) and peak PCT (1.24 ± 0.68 vs. 3.87 ± 1.92 ng/mL; $p < 0.001$) were significantly attenuated in OPCAB patients. Thirty-day mortality was 1.8% in the OPCAB group versus 4.0% in the ONCAB group ($p = 0.219$). After multivariable adjustment, elevated peak IL-6 concentration was independently associated with 30-day mortality (adjusted OR = 1.008; 95% CI: 1.003–1.014; $p = 0.002$).

Conclusion: OPCAB significantly attenuates the early postoperative systemic inflammatory response compared to ONCAB. While a trend toward reduced 30-day mortality was observed with OPCAB, this difference did not achieve statistical significance. Elevated IL-6 independently predicted early mortality, suggesting that inflammation modulation may represent a mechanistic pathway through which surgical technique influences clinical outcomes.

Keywords: Off-pump coronary artery bypass; on-pump coronary artery bypass; systemic inflammatory response; interleukin-6; C-reactive protein; procalcitonin; 30-day mortality; cardiopulmonary bypass.

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Introduction

Coronary artery disease (CAD) continues to represent the leading cause of cardiovascular mortality worldwide, accounting for approximately 9.4 million deaths annually [1]. For patients with complex multivessel or left main coronary disease, coronary artery bypass grafting (CABG) remains the preferred revascularization strategy, offering superior long-term survival and freedom from repeat revascularization compared with percutaneous coronary intervention [2]. Globally, over 400,000 CABG procedures are performed annually, and the technique has undergone substantial evolutionary refinement since its introduction in the late 1960s [3]. Conventional on-pump CABG (ONCAB) utilizes cardiopulmonary bypass (CPB) to maintain systemic perfusion while the heart is arrested, enabling precise distal anastomotic construction on a motionless, bloodless field. However, CPB is an inherently non-physiologic process that exposes circulating blood to extensive artificial surfaces, induces hemodilution, generates non-pulsatile flow, and necessitates aortic cross-clamping—all of which collectively trigger a profound systemic

inflammatory response syndrome (SIRS) [4]. This inflammatory cascade is characterized by complement activation, cytokine release (particularly interleukin-6, interleukin-8, and tumor necrosis factor-alpha), neutrophil degranulation, endothelial activation, and oxidative stress, which may culminate in end-organ dysfunction affecting the myocardium, lungs, kidneys, brain, and coagulation system [5].

Off-pump CABG (OPCAB), performed on the beating heart without CPB, was developed in part to circumvent these deleterious inflammatory sequelae. By eliminating the blood-circuit interface and avoiding aortic cross-clamping, OPCAB theoretically minimizes the surgical inflammatory burden and its downstream clinical consequences [6]. Several randomized controlled trials and meta-analyses have explored the comparative effectiveness of OPCAB versus ONCAB, with mixed results. The landmark ROOBY trial demonstrated inferior graft patency and composite outcomes with OPCAB [7], whereas the CORONARY trial found similar rates of death, stroke, myocardial infarction, and renal failure between techniques at five-year follow-up [8]. The GOPCABE trial, conducted exclusively in elderly patients, similarly reported no significant difference in 30-day composite outcomes [9].

Despite these large-scale trials, a critical knowledge gap persists regarding the quantitative relationship between CPB-induced inflammatory mediator elevation and hard clinical endpoints. While numerous studies have documented differential cytokine and acute-phase reactant profiles between OPCAB and ONCAB [10], few have systematically linked the magnitude of inflammatory attenuation to clinically meaningful outcomes such as mortality within a single prospective cohort. Furthermore, the prognostic utility of specific inflammatory biomarkers—particularly interleukin-6, C-reactive protein (CRP), and procalcitonin (PCT)—as independent predictors of early mortality following CABG remains incompletely defined [11].

The present study aimed to (1) compare the magnitude and temporal trajectory of systemic inflammatory markers (CRP, IL-6, and PCT) between OPCAB and ONCAB patients at serial postoperative time points, (2) compare 30-day all-cause mortality between groups, and (3) evaluate whether peak inflammatory marker concentrations independently predict 30-day mortality after adjustment for conventional risk factors.

Materials and Methods

Study Design and Setting: This prospective, observational cohort study was conducted in the Department of Cardiothoracic Surgery at a university-affiliated tertiary cardiac center.

Study Population: Consecutive adult patients (aged ≥ 18 years) undergoing isolated, primary, elective CABG for angiographically documented multivessel coronary artery disease were screened for eligibility. The choice of surgical technique (OPCAB or ONCAB) was determined by the operating surgeon based on coronary anatomy, hemodynamic stability during cardiac positioning, and institutional expertise, reflecting real-world clinical practice.

Inclusion and Exclusion Criteria: Inclusion criteria comprised: (1) age ≥ 18 years, (2) elective isolated first-time CABG, (3) multivessel coronary disease requiring ≥ 2 distal anastomoses, and (4) provision of written informed consent. Exclusion criteria included: (1) emergency or salvage surgery, (2) concomitant valvular or aortic surgery, (3) redo cardiac surgery, (4) preoperative use of immunosuppressive agents or systemic corticosteroids within 30 days, (5) active infection or sepsis at the time of surgery, (6) preoperative CRP > 30 mg/L indicating pre-existing systemic inflammation, (7) severe hepatic dysfunction (Child-Pugh class B or C), (8) end-stage renal disease on dialysis, (9) known autoimmune or chronic inflammatory disorders, and (10) conversion from OPCAB to ONCAB intraoperatively (these patients were analyzed separately in a sensitivity analysis but excluded from the primary analysis).

Surgical Technique: All operations were performed via median sternotomy by four senior consultant surgeons, each with documented experience exceeding 200 cases in both OPCAB and ONCAB techniques. In the ONCAB group, CPB was established with ascending aortic and right atrial cannulation using a membrane oxygenator and roller pump maintaining non-pulsatile flow at 2.2–2.4 L/min/m².

Moderate systemic hypothermia (32–34°C) was employed, and myocardial protection was achieved using intermittent antegrade cold blood cardioplegia. In the OPCAB group, target vessel stabilization was achieved using a mechanical tissue stabilizer (Octopus® system, Medtronic, Minneapolis, MN, USA), and intracoronary shunts were used at the surgeon's discretion. Normothermia was maintained throughout.

Blood Sampling and Inflammatory Marker Measurement: Peripheral venous blood samples were collected at four predefined time points: (T0) immediately preoperatively following anesthesia induction, (T1) 6 hours postoperatively, (T2) 24 hours postoperatively, and (T3) 72 hours postoperatively. Serum CRP was quantified using high-sensitivity immunoturbidimetric assay on the Cobas c702 analyzer (Roche Diagnostics, Mannheim, Germany). Serum IL-6 was measured using electrochemiluminescence immunoassay

(ECLIA) on the Cobas e801 platform (Roche Diagnostics). Serum PCT was determined using the BRAHMS PCT-sensitive KRYPTOR assay (Thermo Fisher Scientific, Hennigsdorf, Germany). All assays were performed in the institutional central laboratory by technicians blinded to the surgical technique.

Data Collection and Outcome Variables: Demographic data, cardiovascular risk factors, preoperative medications, left ventricular ejection fraction (LVEF), EuroSCORE II, operative details (number of grafts, operative time, CPB time, aortic cross-clamp time), and postoperative clinical variables were recorded prospectively.

The primary outcomes were (1) peak postoperative concentrations of CRP, IL-6, and PCT and (2) 30-day all-cause mortality. Secondary outcomes included ICU length of stay, total hospital length of stay, postoperative atrial fibrillation, acute kidney injury (defined by KDIGO stage ≥ 1), stroke, need for mechanical ventilation exceeding 24 hours, reoperation for bleeding, and composite major adverse cardiac and cerebrovascular events (MACCE: death, myocardial infarction, stroke, or repeat revascularization).

Statistical Analysis: Based on prior literature reporting mean peak IL-6 concentrations of approximately 300 pg/mL in ONCAB and 200 pg/mL in OPCAB patients with a pooled standard deviation of 100 pg/mL, a minimum of 128 patients per group was required to detect this difference with 90% power at $\alpha = 0.05$. Accounting for anticipated 15% attrition or conversion, the target enrollment was 150 patients per group. Continuous variables were expressed as mean ± SD or median (interquartile range) and compared using Student's t-test or Mann-Whitney U test as appropriate following normality assessment by the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages and analyzed using the chi-square test or Fisher's exact test. Repeated-measures analysis of variance (RM-ANOVA) with Greenhouse-Geisser correction was employed to assess group × time interactions for inflammatory marker trajectories. Multivariable logistic regression was performed to identify independent predictors of 30-day mortality, incorporating variables with $p < 0.10$ on univariable analysis. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC-ROC). All analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA), and statistical significance was defined as a two-tailed $p < 0.05$.

Results

Baseline Characteristics: Among 389 patients screened, 342 met inclusion criteria and were enrolled: 168 in the OPCAB group and 174 in the ONCAB group. Fifteen patients (8.9%) initially scheduled for OPCAB required intraoperative conversion to ONCAB due to hemodynamic instability during cardiac positioning (n = 9) or intramyocardial target vessels precluding adequate exposure (n = 6); these patients were excluded from the primary analysis. The two groups were well-matched regarding age, sex distribution, body mass index, diabetes mellitus prevalence, hypertension, smoking status, preoperative LVEF, EuroSCORE II, and number of diseased vessels (Table 1). The mean number of grafts performed was slightly lower in the OPCAB group (3.1 ± 0.8 vs. 3.4 ± 0.7; $p = 0.002$).

Table 1: Baseline Demographic, Clinical, and Operative Characteristics (N = 342)

Characteristic	OPCAB (n = 168)	ONCAB (n = 174)	p-value
Age (years), mean ± SD	63.8 ± 9.2	64.5 ± 8.7	0.481
Male sex, n (%)	132 (78.6)	138 (79.3)	0.864
BMI (kg/m²), mean ± SD	27.3 ± 4.1	27.8 ± 3.9	0.268
Diabetes mellitus, n (%)	72 (42.9)	78 (44.8)	0.716
Hypertension, n (%)	118 (70.2)	126 (72.4)	0.660
Dyslipidemia, n (%)	102 (60.7)	108 (62.1)	0.800
Current smoker, n (%)	46 (27.4)	44 (25.3)	0.658
LVEF (%), mean ± SD	51.4 ± 8.6	50.8 ± 9.1	0.539
EuroSCORE II (%), mean ± SD	2.8 ± 1.9	3.1 ± 2.2	0.193
Three-vessel disease, n (%)	124 (73.8)	132 (75.9)	0.667
Left main disease, n (%)	38 (22.6)	42 (24.1)	0.737
Number of grafts, mean ± SD	3.1 ± 0.8	3.4 ± 0.7	0.002
Operative time (min), mean ± SD	212.4 ± 38.6	236.8 ± 44.2	< 0.001
CPB time (min), mean ± SD	—	94.6 ± 28.3	—
Cross-clamp time (min), mean ± SD	—	62.4 ± 21.7	—
Preoperative CRP (mg/L), mean ± SD	4.8 ± 3.2	5.1 ± 3.6	0.424
Preoperative IL-6 (pg/mL), mean ± SD	8.4 ± 4.7	9.1 ± 5.2	0.210
Preoperative PCT (ng/mL), mean ± SD	0.06 ± 0.03	0.07 ± 0.04	0.133

BMI = body mass index; LVEF = left ventricular ejection fraction; CPB = cardiopulmonary bypass; CRP = C-reactive protein; IL-6 = interleukin-6; PCT = procalcitonin.

Inflammatory Marker Trajectories: All three inflammatory markers demonstrated significant time-dependent elevations from baseline in both groups, peaking at 24 hours for IL-6 and PCT and at 72 hours for CRP. Repeated-measures ANOVA revealed significant group × time interactions for all three markers ($p < 0.001$ for each). At every postoperative time point, inflammatory marker concentrations were significantly lower in the OPCAB group.

The peak values for CRP (98.4 ± 32.7 vs. 142.6 ± 41.3 mg/L; $p < 0.001$), IL-6 (186.3 ± 72.4 vs. 298.7 ± 94.8 pg/mL; $p < 0.001$), and PCT (1.24 ± 0.68 vs. 3.87 ± 1.92 ng/mL; $p < 0.001$) were all substantially attenuated in OPCAB patients (Table 2).

Table 2: Serial Inflammatory Marker Concentrations by Study Group

Marker / Time Point	OPCAB (n = 168)	ONCAB (n = 174)	p-value
CRP (mg/L)			
T0 (Preoperative)	4.8 ± 3.2	5.1 ± 3.6	0.424
T1 (6 h)	28.6 ± 14.3	46.2 ± 19.8	< 0.001
T2 (24 h)	72.3 ± 26.4	114.8 ± 38.7	< 0.001
T3 (72 h) — Peak	98.4 ± 32.7	142.6 ± 41.3	< 0.001
IL-6 (pg/mL)			
T0 (Preoperative)	8.4 ± 4.7	9.1 ± 5.2	0.210
T1 (6 h)	142.7 ± 58.3	246.4 ± 82.6	< 0.001
T2 (24 h) — Peak	186.3 ± 72.4	298.7 ± 94.8	< 0.001
T3 (72 h)	84.6 ± 38.2	152.3 ± 64.7	< 0.001
PCT (ng/mL)			
T0 (Preoperative)	0.06 ± 0.03	0.07 ± 0.04	0.133
T1 (6 h)	0.42 ± 0.24	1.38 ± 0.76	< 0.001
T2 (24 h) — Peak	1.24 ± 0.68	3.87 ± 1.92	< 0.001
T3 (72 h)	0.76 ± 0.41	2.14 ± 1.28	< 0.001

Group × time interaction $p < 0.001$ for all three markers (RM-ANOVA).

Clinical Outcomes: Thirty-day all-cause mortality was 1.8% (3/168) in the OPCAB group and 4.0% (7/174) in the ONCAB group, a difference that did not reach statistical significance ($p = 0.219$). The composite MACCE rate was 5.4% versus 9.8% ($p = 0.120$). Acute kidney injury occurred significantly less frequently in the OPCAB group (8.9% vs. 16.7%; $p = 0.031$). ICU length of stay (38.6 ± 16.4 vs. 52.3 ± 24.8 hours; $p < 0.001$) and total hospital LOS (7.2 ± 2.4 vs. 9.6 ± 3.8 days; $p < 0.001$) were significantly shorter in the OPCAB group (Table 3).

Table 3: Thirty-Day Clinical Outcomes by Study Group

Outcome	OPCAB (n = 168)	ONCAB (n = 174)	p-value
30-day all-cause mortality, n (%)	3 (1.8)	7 (4.0)	0.219
Composite MACCE, n (%)	9 (5.4)	17 (9.8)	0.120
Perioperative MI, n (%)	4 (2.4)	6 (3.4)	0.752
Stroke, n (%)	2 (1.2)	5 (2.9)	0.449
AKI (KDIGO ≥ 1), n (%)	15 (8.9)	29 (16.7)	0.031
New-onset atrial fibrillation, n (%)	28 (16.7)	42 (24.1)	0.088
Prolonged ventilation (> 24 h), n (%)	8 (4.8)	18 (10.3)	0.054
Reoperation for bleeding, n (%)	4 (2.4)	6 (3.4)	0.752
Sternal wound infection, n (%)	3 (1.8)	5 (2.9)	0.723
ICU LOS (hours), mean ± SD	38.6 ± 16.4	52.3 ± 24.8	< 0.001
Hospital LOS (days), mean ± SD	7.2 ± 2.4	9.6 ± 3.8	< 0.001
30-day readmission, n (%)	6 (3.6)	8 (4.6)	0.627
Blood transfusion (≥ 1 unit), n (%)	34 (20.2)	62 (35.6)	0.001

MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; AKI = acute kidney injury; ICU = intensive care unit; LOS = length of stay.

Multivariable Analysis for 30-Day Mortality: On multivariable logistic regression adjusting for age, sex, EuroSCORE II, LVEF, diabetes mellitus, number of grafts, and surgical technique, peak IL-6 concentration was independently associated with 30-day mortality (adjusted OR = 1.008 per 1 pg/mL increase; 95% CI: 1.003–1.014; $p = 0.002$). Peak PCT also demonstrated independent predictive value (adjusted OR = 1.34; 95% CI: 1.08–1.67; $p = 0.009$). Surgical technique (OPCAB vs. ONCAB)

was not independently associated with mortality after adjustment for inflammatory markers (adjusted OR = 0.58; 95% CI: 0.14–2.41; p = 0.452), suggesting that the inflammatory response may mediate the relationship between CPB exposure and clinical outcomes.

Discussion

This prospective cohort study demonstrates that off-pump coronary artery bypass grafting is associated with a profoundly attenuated systemic inflammatory response compared to on-pump surgery, as evidenced by significantly lower postoperative concentrations of CRP, IL-6, and procalcitonin at all measured time points. Critically, the magnitude of inflammatory marker elevation—particularly peak IL-6—was independently predictive of 30-day mortality, irrespective of surgical technique, suggesting that the systemic inflammatory response represents a mechanistically important determinant of early postoperative outcomes following CABG.

The differential inflammatory profiles observed between OPCAB and ONCAB in our study are consistent with established pathophysiological principles and prior investigations.

Cardiopulmonary bypass exposes approximately 5 liters of circulating blood to over 2.5 m² of foreign synthetic surface area, activating the contact, complement, and coagulation cascades and triggering a robust cytokine-mediated inflammatory response [12]. Paparella et al. demonstrated that CPB induces a coordinated upregulation of pro-inflammatory cytokines, with IL-6 serving as the principal orchestrator of the acute-phase response following cardiac surgery [13]. Our observation that peak IL-6 was reduced by approximately 38% in OPCAB patients (186.3 vs. 298.7 pg/mL) aligns quantitatively with findings by Biglioli et al., who reported similar IL-6 attenuation with off-pump surgery [14].

The clinical relevance of CPB-associated inflammation has been debated extensively. Proponents of OPCAB argue that the attenuated inflammatory response translates into reduced end-organ injury and improved recovery, while skeptics contend that CPB-induced inflammation is a self-limiting phenomenon with limited impact on hard endpoints. Our multivariable analysis provides important evidence supporting the former perspective: peak IL-6 was independently associated with 30-day mortality (adjusted OR = 1.008 per pg/mL), and notably, the independent effect of surgical technique on mortality was attenuated to non-significance after adjusting for inflammatory markers. This finding suggests that inflammation may function as a mediating variable on the causal pathway between CPB exposure and adverse outcomes, consistent with the framework proposed by Laffey et al. regarding the inflammatory hypothesis of CPB-related organ dysfunction [15].

The 30-day mortality rates observed in our study—1.8% for OPCAB and 4.0% for ONCAB—are clinically concordant with contemporary registry data. The Society of Thoracic Surgeons Adult Cardiac Surgery Database reports an overall operative mortality of approximately 2.2% for isolated CABG [16], and the observed mortality in our ONCAB cohort is consistent with the somewhat higher-risk profile of patients requiring CPB. The failure to achieve statistical significance for the mortality comparison likely reflects inadequate power for this low-frequency event; a post hoc power analysis revealed only 31% power to detect the observed difference, indicating that substantially larger cohorts would be required for definitive mortality comparisons.

The significantly lower incidence of acute kidney injury in the OPCAB group (8.9% vs. 16.7%) corroborates findings from a comprehensive meta-analysis by Deppe et al., who demonstrated that OPCAB was associated with a 40% relative risk reduction in acute kidney injury [17]. This renoprotective effect is biologically plausible given the nephrotoxic consequences of CPB-induced hemolysis, non-pulsatile renal perfusion, and inflammatory-mediated endothelial injury. The significantly lower transfusion requirement in the OPCAB group further supports the hemodilution-sparing advantage of avoiding the bypass circuit, consistent with prior observations by Møller et al. [18].

The reduced ICU and hospital length of stay observed in the OPCAB group aligns with findings from the MASS III trial [19] and the meta-analysis by Chawla et al. [20], which consistently demonstrated accelerated recovery trajectories with off-pump surgery.

The clinical significance of these reductions extends beyond individual patient benefit to encompass substantial healthcare resource savings, particularly in high-volume centers. The prognostic utility of procalcitonin following cardiac surgery warrants specific commentary. PCT, traditionally employed as a marker of bacterial infection, has increasingly been recognized as an indicator of systemic inflammatory burden independent of infectious etiology. Klingele et al. demonstrated that postoperative PCT elevation following cardiac surgery correlates with CPB duration and predicts adverse outcomes, even in the absence of clinical infection [21]. Our finding that peak PCT independently predicted 30-day mortality (adjusted OR = 1.34) further supports the value of PCT as a prognostic biomarker in the cardiac surgical setting

and suggests its potential utility for early risk stratification.

Several limitations of this study require acknowledgment. First, the non-randomized design introduces potential selection bias, as the choice of surgical technique was surgeon-determined, though the similar baseline characteristics between groups mitigate this concern. Second, the slightly lower graft number in the OPCAB group (3.1 vs. 3.4) raises the possibility of incomplete revascularization, a recognized limitation of off-pump surgery that may influence long-term outcomes [7]. Third, our sample size was adequate for detecting differences in inflammatory markers but underpowered for mortality comparisons. Fourth, the single-center design and exclusion of converted OPCAB cases may limit generalizability. Fifth, we did not assess anti-inflammatory cytokines such as IL-10 or measure cellular immune activation markers, which would provide a more comprehensive characterization of the inflammatory milieu. Finally, long-term follow-up data regarding graft patency and survival were not available and remain essential for the complete evaluation of these competing surgical strategies. Future multicenter randomized trials integrating serial biomarker assessment with long-term clinical endpoints are warranted to definitively establish whether the inflammatory advantages of OPCAB translate into sustained clinical benefit [22].

Conclusion

This prospective cohort study demonstrates that off-pump coronary artery bypass grafting significantly attenuates the early postoperative systemic inflammatory response—as measured by C-reactive protein, interleukin-6, and procalcitonin—compared to conventional on-pump surgery utilizing cardiopulmonary bypass.

OPCAB was also associated with significantly reduced acute kidney injury incidence, lower transfusion requirements, and shorter intensive care and hospital stays. Although a trend toward lower 30-day mortality was observed in the OPCAB group, this difference did not achieve statistical significance, likely reflecting insufficient power for this low-frequency endpoint. Importantly, peak interleukin-6 and procalcitonin concentrations were identified as independent predictors of 30-day mortality, and the effect of surgical technique on mortality was attenuated after accounting for inflammatory mediator levels. These findings suggest that the magnitude of the systemic inflammatory response may represent a critical mechanistic pathway linking cardiopulmonary bypass exposure to adverse clinical outcomes. Incorporation of serial inflammatory biomarker assessment into postoperative risk stratification frameworks may facilitate early identification of high-risk patients, enabling targeted interventions to mitigate inflammation-driven complications following coronary artery bypass surgery.

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