Perioperative Outcomes, Transfusion Requirements, and Inflammatory Response After Coronary Artery Bypass Grafting With Off-Pump, Mini-Extracorporeal, and On-Pump Circulation Techniques

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Objectives: Mini-extracorporeal circulation (MECC) units were developed to reduce postoperative morbidity, transfusion requirements, and inflammation associated with conventional on-pump coronary artery bypass (ONCAB) surgery without the technical demands of the off-pump (OPCAB) technique. We compared perioperative outcomes and inflammatory mediation among OPCAB, MECC, and ONCAB techniques.

Methods: We prospectively enrolled 102 patients undergoing elective isolated coronary bypass grafting. Perfusion methods were OPCAB (n = 34), MECC (n = 34), and ONCAB (n = 34). Serial blood samples were collected to measure serum inflammatory markers.

Results: There were no operative deaths or strokes. Total red blood cell (RBC) products used in OPCAB, MECC, and ONCAB patients were 0.676, 1.000, and 1.235 units, respectively. Adjusted (by splined Society of Thoracic Surgeons operative risk score) analysis showed no statistically significant differences in mean RBC product use among the different operative systems (OPCAB vs MECC, $P = 0.580$; OPCAB vs ONCAB, $P = 0.311$; MECC vs ONCAB, $P = 0.633$). Adjusted (by Society of Thoracic Surgeons risk score and baseline level) mean plasma level differences (24 hours postoperative - baseline) of C-reactive protein for OPCAB (117.89; 95% confidence interval [95% CI], 106.23–129.54) and for MECC (124.88; 95% CI, 113.45–136.32) were significantly higher than for ONCAB (98.82; 95% CI, 86.40–111.24). No significant adjusted differences ($P = 0.304$) in interleukin-6 level changes were observed.

Conclusions: Off-pump coronary artery bypass and MECC did not significantly reduce mean total RBC transfusion requirements. Off-pump coronary artery bypass and MECC were associated with greater C-reactive protein elevation than ONCAB, suggestive of an increased inflammatory response to each of these techniques.

Key Words: coronary artery bypass grafting, mini-extracorporeal circulation, off-pump coronary artery bypass, conventional cardiopulmonary bypass

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A major source of morbidity and mortality associated with coronary artery bypass graft (CABG) surgery is postoperative systemic inflammatory response syndrome (SIRS).[1] Although the use of cardiopulmonary bypass (ONCAB) is implicated in inducing SIRS,[2] off-pump (OPCAB) CABG technique is not widely performed because of its greater technical demands on surgeons.[3] Recently, mini-extracorporeal circulation (MECC) was developed with the aim of reducing the morbidity associated with ONCAB without invoking the technical demands of the OPCAB technique.[4] Mini-extracorporeal circulation eliminates the standard on-pump venous reservoir and direct suction return while implementing a closed circuit to minimize blood-air interface, circuit size, priming volume, hemodilution, and mechanical blood trauma.[5] We compared perioperative outcomes, transfusion requirements, and inflammatory mediation among the OPCAB, MECC, and ONCAB perfusion techniques.

MATERIALS AND METHODS

From February 2010 to October 2011, 102 patients undergoing elective isolated CABG for operative technique (OPCAB, n = 34; MECC, n = 34; and ONCAB, n = 34) at The Heart Hospital Baylor Plano (Plano, TX) were prospectively and consecutively enrolled in this institutional review board–approved study (no. 009-113, approved June 6, 2009). Patients with contraindications for the use of cardiopulmonary bypass or the use of heparin were excluded. Given ethical limitations restricting our ability to assign patients to bypass techniques via randomization, patients were instead assigned according to surgeon preference. Patients were enrolled consecutively to limit possible selection bias. Rigorous statistical analysis as described below was performed to ensure a quasi-randomization of the patient cohorts for comparison between bypass techniques.

All procedures were performed via a median sternotomy approach. When using either MECC or ONCAB for cardiopulmonary bypass, the arterial cannulation site was the ascending aorta with venous drainage from the right atrium. Conventional arterial and venous cannulae were used. Standard anesthetic techniques were used for all groups and were not altered by the study protocol.

The MECC unit was a closed-loop circuit (ie, no cardiotomy venous reservoir) (Maquet Ltd, Sunderland, United Kingdom). Blood was drained from the right atrium and passed through a centrifugal pump, a membrane oxygenator with integrated heat exchanger, and back into the ascending aorta. A bubble trap with alarm was integrated into the venous line to allow evacuation of unwanted air from the circuit. No cardiotomy suckers were used in the MECC units. The MECC prime volume was 1000 mL before retrograde autologous priming (RAP). To further reduce hemodilution during MECC, cardioplegia was used. Each dose of cardioplegia used tepid blood from the oxygenator with a steady infusion of potassium chloride and magnesium sulfate from a 60-mL syringe for 2 minutes of infusion. The ONCAB circuits used standard cannulae and a traditional "open" cardiopulmonary bypass circuit with a cardiotomy reservoir. Cardioplegia was also implemented in ONCAB cases.

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Preoperative, perioperative, and postoperative data (including red blood cell [RBC] use) were recorded, and serial blood samples were collected at specified time points: preoperative (baseline), skin closure, and 24 hours postoperatively. Serum interleukin-6 (IL-6) and C-reactive protein (CRP) values were measured per standard laboratory protocols.

Means, SDs, and percentages were calculated to describe the study cohort. Differences in demographic, clinical, and morphological details were tested using a Wilcoxon (for continuous factors) or a χ^2 (for categorical factors) test. Unadjusted P values and 95% confidence intervals (95% CIs) were also estimated. A general linear model adjusted by the Society of Thoracic Surgeons (STS) risk score[6] was used to assess the association between the different operative systems and total RBC units used.

The same approach was used to assess the association between the different operative systems and inflammatory marker (IL-6 and CRP) level differences (24 hours - baseline). However, in this case, the general linear model also accounted for IL-6 and CRP baseline levels. By adjusting the statistical analyses with the STS score, the resulting analysis warrants a robust and rigorous adjustment for the patients' case-mix among the 3 study groups, the next best option given that true randomization could not be performed.

The STS risk score was modeled by using restricted cubic splines to avoid some of the dangers involved in categorization and to obviate the need to assume a linear effect for the STS risk score.[7] Complete case analyses were executed given that outcomes data were missing for only 5 observations (<5%). The adjusted means and 95% CI were estimated using the model results. Results for continuous variables are reported as mean ± SD in the text.

RESULTS

Table 1 shows patients' characteristics. Mean STS predicted risk scores of mortality in OPCAB, MECC, and ONCAB were 0.9%, 1.2%, and 1.9%, respectively. All 102 patients were discharged alive, and there were no adverse neurologic events observed during hospitalization.

Table 2 summarizes RBC product usage by operative system. Adjusted total mean RBC product use for each operating system was as follows: MECC, 0.949 (95% CI, 0.520–1.377); OPCAB, 0.777 (95% CI, 0.341–1.213); and ONCAB, 1.098 (95% CI, 0.650–1.546). Adjusted analysis showed no statistically significant differences in total mean RBC product use between the different operative systems: ONCAB versus MECC (P = 0.633); ONCAB versus OPCAB (P = 0.311); MECC versus OPCAB (P = 0.580) (Fig. 1).

Table 3 summarizes trends in serum IL-6 and CRP levels by operative system and time point. Levels of IL-6 were increased from preoperative baseline by the time of skin closure in all

TABLE 1. Preoperative Risk Data Comparison Between Study Groups

Characteristic	OPCAB (n = 34)	MECC (n = 34)	ONCAB (n = 34)	P†
STS predicted risk of mortality (median, IQR)	0.7% (0.4%–1.1%)	0.8% (0.4%–1.3%)	0.9% (0.5%–1.2%)	0.596
Age, y	62.8 ± 9.8*	63.7 ± 10.5*	66.4 ± 9.2*	0.416
Body mass index, kg/m^2	29.5 ± 4.8*	28.3 ± 5.9*	29.7 ± 7.3*	0.468
Race				0.325
White	85.3%	91.2%	94.1%	
Black	11.8%	5.9%	0%	
Asian	2.9%	2.9%	5.9%	
Diabetes mellitus	39.4%	44.1%	35.3%	0.758
Creatinine, mg/dL	1.2 ± 0.4*	1.3 ± 1.3*	1.1 ± 0.4*	0.395
Chronic lung disease	11.8%	11.8%	8.8%	0.674
Systemic hypertension	79.4%	91.2%	85.3%	0.391
Peripheral vascular disease	11.8%	11.8%	17.7%	0.718
Cerebrovascular disease	8.8%	11.8%	11.8%	0.903
Time from last myocardial infarction to surgery				0.478
None	82.4%	70.6%	55.9%	
>6 but <24 h	0%	0%	2.9%	
1 to 7 d	0%	11.8%	11.8%	
8 to 21 d	0%	2.9%	2.9%	
>21 d	17.6%	14.7%	26.5%	
Congestive heart failure	8.8%	5.9%	5.9%	0.858
Previous coronary bypass	0%	2.9%	0%	0.403
Previous PCI	32.4%	29.4%	29.4%	0.487
Preoperative ejection fraction, %	52.6 ± 13.9*	56.1 ± 10.9*	53.4 ± 13.0*	0.647
Preoperative left main narrowing	11.8%	32.4%	38.2%	0.037
Preoperative IABP	0%	0%	2.9%	0.364
Operation				0.002
Elective	88.2%	50.0%	76.5%	
Nonelective	11.8%	50.0%	23.5%	

*Mean ± SD.

†Continuous variables with χ^2 test and continuous variables with Wilcoxon signed rank test.

IABP indicates intra-aortic balloon pump; IQR, interquartile range; PCI, percutaneous coronary intervention.

TABLE 2. RBC Product Use Between OPCAB, MECC, and ONCAB

		Operative			Postoperative			Total		
Method	n	Units*	Minimum	Maximum	Units*	Minimum	Maximum	Units*	Minimum	Maximum
OPCAB	34	0.147 ± 0.500	0	2	0.529 ± 0.960	0	4	0.676 ± 1.120	0	4
MECC	34	0.264 ± 0.665	0	2	0.735 ± 1.213	0	5	1.000 ± 1.435	0	5
ONCAB	34	0.470 ± 0.928	0	3	0.764 ± 1.577	0	7	1.235 ± 1.724	0	7

*Mean ± SD.

3 groups (Fig. 2A). Adjusted analysis showed no significant ($P = 0.304$) differences in IL-6 level changes between operating systems at skin closure or at 24 hours postoperatively. Adjusted mean plasma level differences (24 hours - baseline) of IL-6 for each operating system were MECC, 15.280 (95% CI, 11.061–19.500); OPCAB, 14.212 (95% CI, 9.918–18.506); and ONCAB 18.980 (95% CI, 14.363–23.596).

Increases in IL-6 levels were followed by increases in CRP levels (reported as mean ± SD) by 24 hours postoperatively in all 3 groups (Fig. 2B). Adjusted mean plasma level differences (24 hours - baseline) of CRP for MECC (124.88; 95% CI, 113.45–136.32) and for OPCAB (117.89; 95% CI, 106.23–129.54) were significantly higher than for ONCAB (98.82; 95% CI, 86.40–111.24) (Fig. 3).

DISCUSSION

Few studies have compared OPCAB, MECC, and ONCAB concurrently.[8,9] In this series of 102 patients undergoing CABG at a single institution, there were no operative mortalities or perioperative neurological complications. This study adds to the consensus that the MECC technique is appropriately safe for CABG surgery.[10]

Although the raw data suggested increasing total mean RBC product use in moving from OPCAB to MECC to ONCAB, no statistically significant differences were apparent after adjustment. Other studies have demonstrated similar results between OPCAB and MECC.[11,12] Some studies have concluded that MECC reduces transfusion rates compared with ONCAB, but these did not adjust for STS risk score as we did.[8,13]

Interleukin-6 and CRP are routinely measured in research studies to investigate the postoperative inflammatory response to cardiac surgery.[14] Several previous studies have investigated plasma level differences (postoperative - preoperative) in IL-6 and CRP between OPCAB and MECC[9,11,15,16] or MECC and ONCAB,[5] all of which failed to demonstrate significance. Our study is the first that has compared serum inflammatory marker levels after adjusting for STS risk score. Levels of the acute-phase reactant IL-6 were increased from preoperative baseline by the time of skin closure in each group. Serum CRP levels were elevated by 24 hours postoperatively. These trends are consistent with previous studies of inflammatory markers after surgery[17] and demonstrate that all 3 CABG techniques were associated with a marked inflammatory response. No statistically significant differences in adjusted mean plasma level differences in IL-6 were detected across the 3 groups. However, adjusted mean plasma level differences (24 hours - baseline) in CRP were significantly increased in both OPCAB and MECC compared with ONCAB.

The clinical significance of this result is not immediately clear. Several studies have connected elevated preoperative CRP levels with adverse outcomes in both OPCAB and ONCAB,[18,19] and elevated postoperative CRP levels have been linked to adverse outcomes and complications in a variety of noncardiac surgeries.[20] However, there were no operative mortalities or adverse

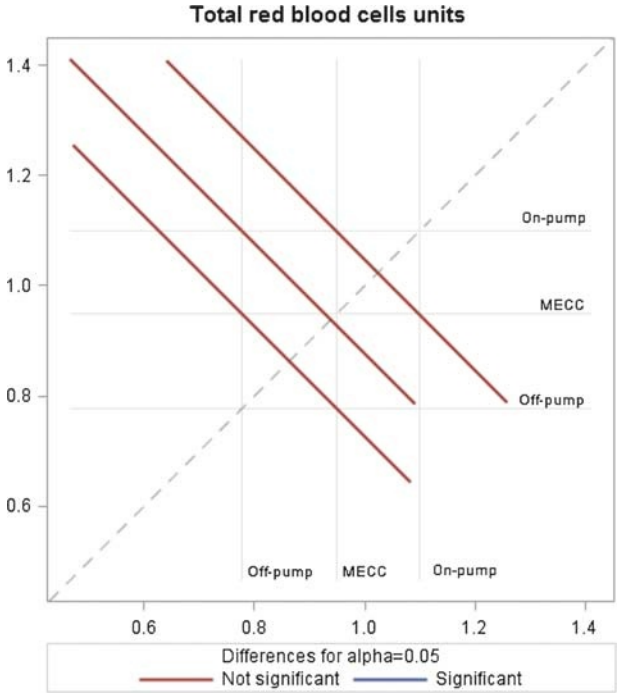

FIGURE 1. Mean-mean scatter plot representing differences in adjusted (by STS risk score) mean total RBC units used between pairs of operative systems. Points of intersection between vertical and horizontal lines represent value of difference in RBC usage between corresponding systems. Solid lines represent 95% CIs of differences. No significant differences between pairs of operative systems were evident 24 hours after surgery.

TABLE 3. Unadjusted IL-6 and CRP Serum Levels at Preoperative (Baseline), Skin Closure, and 24-Hour Postoperative Time Points for Each Cohort

Technique	Time Point	IL-6, μg/L*	CRP, mg/L*
OPCAB	Preoperative	5.2 ± 6.9	12.9 ± 14.3
	Skin closure	18.1 ± 8.1	9.4 ± 13.0
	24 h postoperative	19.8 ± 11.5	133.1 ± 28.5
MECC	Preoperative	5.9 ± 5.8	14.4 ± 22.8
	Skin closure	21.8 ± 11.8	9.4 ± 14.6
	24 h postoperative	20.3 ± 12.5	140.0 ± 29.4
ONCAB	Preoperative	4.0 ± 4.4	14.7 ± 30.4
	Skin closure	23.5 ± 12.1	6.6 ± 9.1
	24 h postoperative	23.2 ± 12.1	115.5 ± 39.8

*Mean ± SD.

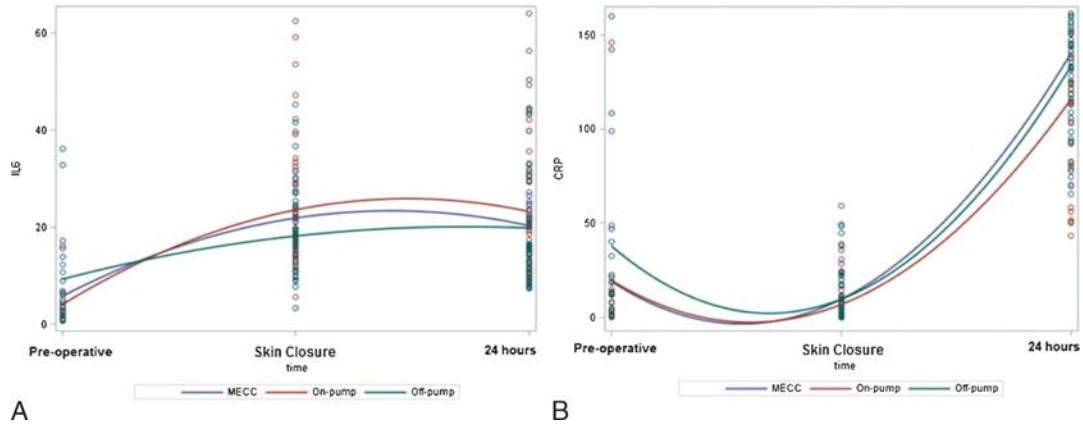

FIGURE 2. Interleukin-6 (A) and CRP (B) levels from preoperative (baseline), skin closure, and 24-hour postoperative time point measurements by operative system.

neurological complications in any group during hospitalization in this study.

Limitations of this study include those expected of a single-center prospective protocol. This study assessed only 2 of the hundreds of potential serum inflammatory markers currently available to clinicians,[14] and measurement of the markers was only performed for a 24-hour postoperative period. Further studies are necessary to determine whether differences in postoperative serum inflammatory marker levels persist beyond 24 hours and if the duration of SIRS induced by CABG, which can be more than 72 hours, is dependent on technique. Longer-term follow-up is also necessary to determine what effects, if any, degree of SIRS has on patient outcomes after discharge from the hospital.

In conclusion, CABG induces a marked inflammatory response, but there were no adverse outcomes in any cohort during hospitalization. No significant differences in total RBC product transfusion were demonstrated between bypass techniques. Although the postoperative rise in adjusted serum IL-6 levels was not significantly different in any group, OPCAB and MECC were associated with a significantly increased rise in adjusted plasma CRP levels postoperatively. This finding is suggestive that OPCAB and MECC might be associated with an increased inflammatory response after CABG.

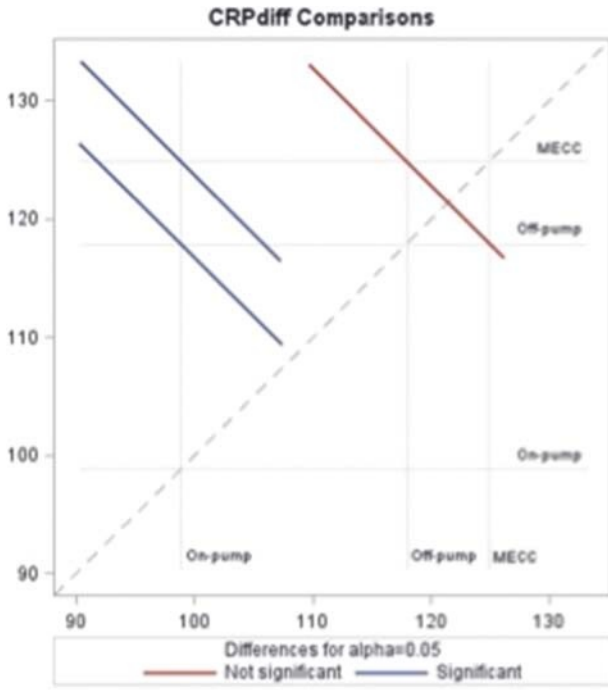

FIGURE 3. Mean-mean scatter plot representing differences in adjusted (by STS risk score) mean CRP level differences (24 hours - baseline) between pairs of operative systems. Points of intersection between vertical and horizontal lines represent value of difference in mean CRP level differences between corresponding systems. Solid lines represent 95% CIs of differences. Red lines represent nonsignificant differences, whereas blue lines represent statistically significant differences between operative systems. C-reactive protein levels were less elevated in ONCAB compared with both OPCAB and MECC 24 hours after surgery.

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