Systemic and Myocardial Inflammatory Response in Coronary Artery Bypass Graft Surgery With Miniaturized Extracorporeal Circulation: Differences With a Standard Circuit and Off-Pump Technique in a Randomized Clinical Trial

Francesco Formica,* Silvia Mariani,* Francesco Broccolo,† Rosa Caruso,‡ Fabrizio Corti,* Stefano D'Alessandro,* Pietro Amigoni,* Fabio Sangalli,§ and Giovanni Paolini*

Inflammatory response and hemodilution are the main drawbacks of extracorporeal circulation. We hypothesize that the use of miniaturized extracorporeal circulation (MECC) might lower the systemic and myocardial inflammatory patterns compared with a standard system (SECC) and off-pump coronary artery bypass grafting (OPCABG). Sixty-one patients undergoing isolated coronary artery bypass graft were prospectively randomized to MECC (n = 19), SECC (n = 20), or OPCABG (n = 22). Blood samples were collected from radial artery and coronary sinus to analyze blood lactate, hemodilution, and markers for inflammation and endothelial activation such as tumor necrosis factor (TNF)-α, interleukin-6, monocyte chemotactic protein-1, and E-selectin. No differences were observed in early clinical outcome. Interleukin -6 levels increased in every group during and after cardiac surgery, whereas TNF-α values grew in the SECC group ($p = 0.05$). E-selectin systemic values decreased during and after operation ($p = 0.001$) in every group. Monocyte chemotactic protein-1 systemic and cardiac levels raised only in SECC group ($p = 0.014$). In conclusion, MECC is comparable to SECC and OPCABG in the clinical outcome of low-risk patients, and it might be extensively used with no additional intraoperative risk. The analysis of the inflammatory patterns of endothelial activation shows MECC as effective as OPCABG, suggesting further studies to clarify MECC recommendation in high-risk patients. *ASAIO Journal* 2013; 59:600–606.

Key Words: cardiopulmonary bypass, miniaturized extracorporeal circulation, coronary artery bypass grafts, cytokines, inflammation

From the *Cardiac Surgery Clinic, Department of Surgical Science and Interdisciplinary Medicine, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy; †Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milan, Italy; ‡Cardiac Surgery Perfusion Service, San Gerardo Hospital, Monza, Italy; and §Cardiothoracic and Vascular Anaesthesia Intensive Care Unit, San Gerardo Hospital, Monza, Italy.

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Reprint Requests: Francesco Formica, MD, Clinica Cardiochirurgica, Ospedale San Gerardo, via Pergolesi, 33-20900 Monza (MB), Italy. Email: francesco_formica@fastwebnet.it.

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Despite improvements in perfusion techniques and surgery, systemic inflammatory response syndrome (SIRS), coagulation disorders, and hemodilution represent some of the main complications related to cardiopulmonary bypass (CPB). Off-pump coronary artery bypass grafting (OPCABG) has been described as an alternative option to on-pump surgery. However, OPCABG has some drawbacks such as incomplete revascularization, low graft patency, and hemodynamic instability that occurs during heart displacement.[1] New CPB designs have been developed, and efforts are focused on the reduction of the tubing surface area, the improvement of the surface coating, the elimination of blood–air contact, and the optimization of oxygenators.

Miniaturized extracorporeal circulation (MECC) is one of the most widespread new CPB systems in order to decrease CPB complications and avoid OPCABG drawbacks. Literature shows that MECC decreases inflammatory response, hemodilution, blood transfusions, and organ damage when compared with standard extracorporeal circulation (SECC).[2–6]

In our previous study, we analyzed plasma levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α, and we demonstrated that MECC and OPCABG should be considered as similar in terms of early outcome, SIRS, myocardial inflammation, and damage.[7] The latest literature has focused on peculiar features of CPB-related systemic and myocardial inflammatory response like endothelial cell activation and production of soluble cytokines. In spite of that, the effects of those patterns on clinical outcomes are still unknown. Nevertheless, very little is known about the effect of the MECC technique on the endothelial function compared with SECC and OPCABG.

In the present trial, we hypothesize that MECC induces a lower systemic and cardiac inflammatory response and a lower endothelial activation compared with SECC in terms of release of inflammatory markers like monocyte chemotactic protein (MCP)-1 and E-selectin. On the other hand, we expect to get similar results from MECC and OPCABG. OPCABG was considered as control group.

Monocyte chemotactic protein-1 is a chemokine produced by the activated endothelium due to inflammation. Monocyte chemotactic protein-1 plays a role in the leukocytes attraction and in the recruitment of monocytes in the infarcted myocardium in the first 5 hours after reperfusion.[8] We assume the MCP-1 as a marker of systemic endothelial activation and myocardial inflammation after ischemia. E-selectin is a glycoprotein synthesized by activated endothelial cells. It binds neutrophils and other leukocytes in the early stages of acute

inflammation. Due to its minimal expression on resting endothelial cells, membrane and soluble forms of E-selectin are effective markers of endothelial activation.[9]

We conceived a prospective randomized study in order to test our hypothesis on low-risk patients undergoing isolated coronary artery bypass grafting (CABG) through MECC, SECC, or OPCABG.

Methods

Patient Population

Between June and December 2011, 61 consecutive patients undergoing isolated CABG operation at San Gerardo Hospital were enrolled in our prospective parallel group randomized trial. All patients who were technically suitable for on-pump or off-pump revascularization were assigned to three groups according to randomization protocol: standard extracorporeal circulation (SECC group, n = 20), miniaturized CPB (MECC group, n = 19), and off-pump CABG (OPCABG group, n = 22). Patients selection was based on the following criteria: first and isolated CABG operation, at least two-vessel disease, ejection fraction equal or more than 40%, age between 18 and 85 years, serum creatinine levels lower than 1.8 mg/100 ml, absence of inflammatory syndromes, and hematological disorders. Exclusion criteria were calcified and intramyocardial coronary arteries, recent or current steroid treatments, emergency or urgency operation, recent myocardial infarction (<10 days), unstable angina with intravenous medications, and preoperative intra-aortic balloon pump (IABP). Local Ethics Committee approved this study, and a written consent was obtained from every patient.

Anesthetic Management and Surgical Strategy

All patients were given the same anesthesia protocol. Anesthesia was induced with fentanyl 0.005–0.01 mg/kg, midazolam 0.08–0.2 mg/kg, and rocuronium 0.6 mg/kg. It was maintained with propofol 3–6 mg/kg/h, fentanyl, sevoflurane, and rocuronium as needed. Tranexamic acid was administered as a continuous infusion to reduce blood loss.

Surgery was performed through a full median sternotomy. The left internal thoracic artery (left ITA) was harvested in all patients, and it was always anastomosed to the left anterior descending artery (LAD).

CPB Management and Off-Pump Technique

The standard extracorporeal system consisted of a polyvinylchloride heparin-coated circuit (Maquet-Jostra, Hirrlingen, Germany), an hollow-fiber polypropylene oxygenator (Quadrox Maquet-Jostra, Hirrlingen, Germany), an open reservoir, a roller pump (Stockert, Munchen, Germany), a system of blood suction from the surgical field, a heat exchanger, and an arterial filter Maquet-Jostra (Hirrlingen, Germany). The CPB circuit was primed with 1,500 ml of saline solution, and no retropriming was used. Heparin was given in order to obtain an activated clotting time (ACT) of 480 sec.

The MECC system (Maquet-Jostra AG, Hirrlingen, Germany) was a closed miniaturized circuit with no blood–air contact and no open venous reservoir. The system components included a centrifugal Rotaflow pump, a polimethylpentene membrane QuadroxD oxygenator, a heat exchanger, a venous bubble trap VBT160 located between the venous line and the centrifugal pump, an arterial filter, and a 1,000 ml closed bag used to prime and substitute volume during CPB. Tubing section was 3/8 inch with a length range between 1 m and 1.5 m. A suction vent was positioned in the aortic root, and it was linked to the venous line through a one-fourth inch tube and a Y-shaped connector. All components were heparin coated. The MECC circuit was primed in the same way as the SECC one. Retropriming was used, and the effective priming volume was about 650 ml. Heparin was given in order to achieve an ACT of 350–400 sec. Heparinization was reversed with protamine sulfate (1 mg per 100 UI of heparin) so to reach an ACT within 10% of baseline level in both SECC and MECC groups.

CPB was achieved by aortic and right atrial cannulation. A venous two-stage cannula was used. All on-pump operations were performed under mild systemic hypothermia (35°C), and a cardiac index of 2.4 L/min/m^2 with a mean pressure about 60 mm Hg was kept during CPB. We induced and maintained cardiac arrest through the use of intermittent blood cold (4°C) cardioplegia administered via the aortic root and coronary sinus. We repeated cardioplegia administration every 20 minutes according to Buckberg's protocol. All distal and proximal anastomoses were performed under a single total aortic cross-clamping time. In the MECC group, the proximal anastomosis in the aortic root was made after clamping of the aortic root vent.

In the OPCABG group, heparin (1.5 mg/kg) was administered to obtain an ACT target of 250 sec. The anastomosis between the left ITA and the LAD artery was always performed as first. The proximal anastomosis in the aortic root was done with the HeartString II Proximal Seal System device (Maquet AG, Hirrlingen, Germany). The distal anastomosis on the marginal branches and the right coronary were done in the end. The heart was stabilized with the Octopus device (Medtronic, Minneapolis, MN). An Axius intracoronary shunt (Maquet, Hirrlingen, Germany) was used. All the operations were performed by the same senior surgeon.

All the pericardial suction blood was collected into a cell saver (CAIS Hemocare Fresenius, Bad Homburg, Germany) and reinfused in both MECC and OPCABG patients. In the SECC group, the blood from surgical field and aortic root was directed into the venous reservoir during CPB and into a cell saver after heparin neutralization.

Samples Collection

Blood samples were collected from the radial artery so to analyze the systemic inflammatory response, blood lactate, hemoglobin, and hematocrit levels at seven time points. Cytokines, blood lactate, and hemodilution levels were simultaneously analyzed also in the coronary sinus (CS) at three points in time as shown in **Figure 1**. A CS cannula for cardioplegia delivery (Edwards Lifesciences, Irvine, CA) was used to collect blood samples. In the OPCABG group, the CS cannula was placed just for blood sampling.

Markers for inflammatory response were TNF-α, IL-6, MCP-1, and E-selectin. Samples were immediately cooled, centrifuged, and the supernatant was separated and stored at −80°C. Cytokine concentrations were determined using ELISA kits (DuoSet ELISA, R&D System, Minneapolis, MN). All the

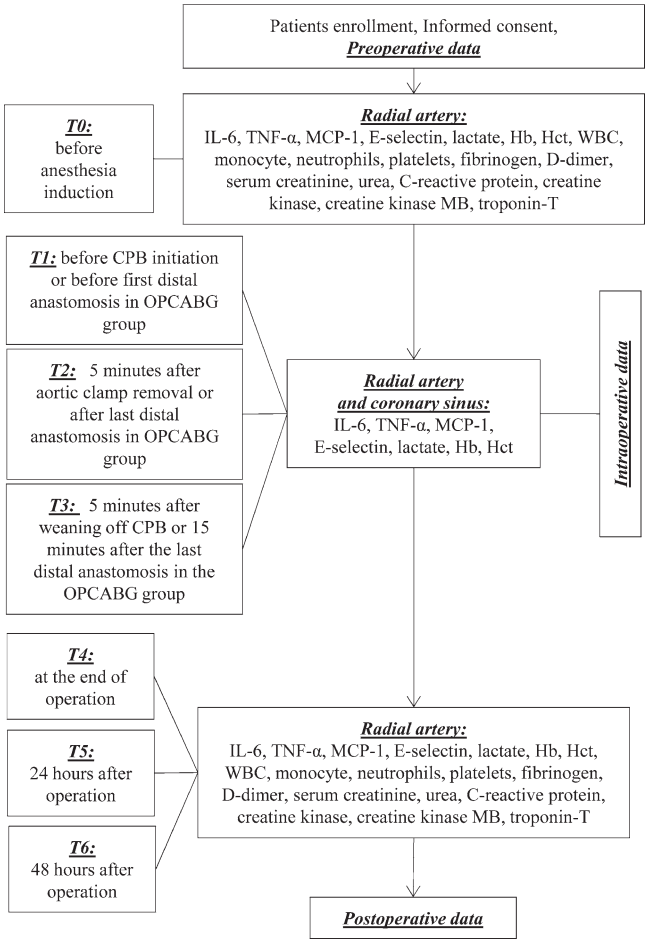

Figure 1. Clinical trial flow chart: blood sample and data collection. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; MCP-1, monocyte chemotactic protein-1; Hb, hemoglobin; Hct, hematocrit; WBCs, white blood cells; CPB, cardiopulmonary bypass; OPCABG, off-pump coronary artery bypass graft.

analyses were done in duplicate with a minimum detectable dose of 5.0 pg/ml for TNF-α and MCP-1, 15.0 pg/ml for IL-6 and 90.0 pg/ml for E-selectin.

Other biochemical laboratory investigations were collected as shown in **Figure 1**. Measurements of troponin-T and CK-myocardial band (MB) were based on electrochemiluminescence immunoassay technology; an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany) was used. The detection limit was 0.01 mg/L for troponin-T and 0.1 mg/L for CK-MB. Except for hemoglobin and hematocrit, the concentrations of all other plasma variables were corrected as follows:

$$\text{Corrected measurement} = \text{measurement} \times (\text{baseline hematocrit}/\text{measured hematocrit}).$$

Variable Definitions

Primary endpoints were perioperative mortality and morbidity. An electrocardiogram was recorded after admission to the intensive care unit, and a continuous electrocardiographic monitoring was maintained during postoperative stay. Atrial fibrillation was defined as the absence of P waves and electrocardiographic evidence of fibrillatory atrial waves with an irregular ventricular response whenever the atrio-ventricular conduction is normal. New myocardial infarction was defined as new Q waves of more than 0.05 mV and a reduction in R waves of more than 25% in at least two electrocardiogram leads, as well as new echocardiographic akinetic or hypokinetic areas. Indication for packed red cells (PRCs) transfusion was hemoglobin <6 g/dl during CPB and <8 g/dl after CPB and during postoperative stay. We considered hospital discharge as either rehabilitation facilities or home. Secondary endpoints were the differences in systemic and cardiac concentrations of inflammatory biomarkers IL-6, TNF-α, MCP-1, and E-selectin.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical data were presented as frequency counts and percentage (N, %). Chi-square test or Fisher's exact test was applied to compare clinical variables. One-way analysis of variance was used for continuous variables; the Kruskal–Wallis test was used for the variables that were not normally distributed. Analysis of continuous variables over time was performed by applying the two-way analysis of variance for repeated measures. A p value <0.05 was considered significant. We applied a per protocol analysis. All data were prospectively included in a database and analyzed with the Statistical Package for the Social Sciences 19.0 (SPSS Inc, Chicago, IL).

Results

Demographic Data and Clinical Outcomes

All patients were discharged from hospital. Two patients in the OPCABG group were withdrawn from the trial because of intraoperative conversion of OPCABG to standard CPB after hemodynamic instability. Preoperative characteristics (**Table 1**) did not differ among the three groups, and there were no differences in preoperative medications among patients. Aspirin was always withdrawn five or more days before surgery. Intraoperative data (**Table 2**) were also similar except for the lowest ACT, which was significantly lower in the MECC group. The cell saver blood volume was lower in the OPCABG group. No patient needed rethoracotomy due to bleeding, and no postoperative cerebrovascular events, low cardiac output syndrome, need for IABP, or acute renal failure occurred.

Myocardial Damage

No postoperative myocardial infarction occurred. Systemic troponin-T values increased in every group at the end of the operation (T4), and there was a significant difference among patients with lower values in OPCABG group (SECC 0.33 ± 0.25 ng/ml; MECC 0.24 ± 0.14 ng/ml; OPCABG 0.09 ± 0.05 ng/ml; $p = 0.001$). This difference disappeared during the first postoperative day: troponin-T values peaked at 24 hours (T5) and decreased 48 hours after the operation (T6) without differences among groups. Levels of CK-MB increased at the end of the operation (T4) with lower values in OPCABG patients (SECC 22.5 ± 10.5 mg/L; MECC 21.7 ± 8.8 mg/L; OPCABG 9.4 ± 3.8 mg/L; $p < 0.001$). This difference disappeared during the first postoperative day (T5), and CK-MB started to decrease 48 hours after the operation (T6) but with no differences among the groups.

Table 1. Baseline Patient Characteristics

Variables	SECC (n = 20)		MECC (n = 19)		OPCABG (n = 20)		*p*
Gender (male), n (%)	13	(65%)	15	(78.9%)	12	(60%)	0.425
Mean age (years)	68.3 ± 9.0	(46–81)	69.9 ± 8.7	(49–83)	70.8 ± 7.0	(56–83)	0.635
Body surface area (m^2)	1.85 ± 0.2	(1.5–2.2)	1.84 ± 0.17	(1.5–2.1)	1.8 ± 0.2	(1.6–2.2)	0.592
Body mass index (kg/cm^2)	26.9 ± 3.2	(21.9–34)	26.1 ± 3.4	(19.9–32.9)	26.8 ± 3.8	(21–38)	0.721
Logistic EuroSCORE	4.1 ± 3.9	(0.9–16.9)	3.3 ± 2.1	(0.9–8.6)	5.5 ± 5.6	(1.3–23.8)	0.257
Ejection fraction (%)	54.7 ± 7.3	(38–63)	56.3 ± 6.7	(46–68)	53.9 ± 8.2	(40–66)	0.591
Vessel disease	2.8 ± 0.4	(2–3)	2.8 ± 0.4	(2–3)	2.7 ± 0.5	(2–3)	0.611
Left main disease, n (%)	7	(35%)	4	(21.1%)	5	(25%)	0.598
Hypertension, n (%)	17	(85%)	17	(89.5%)	15	(75%)	0.465
Diabetes mellitus, n (%)	7	(35%)	3	(15.8%)	9	(45%)	0.405
Current smoke, n (%)	7	(35%)	4	(21.1%)	4	(20%)	0.803
Dyslipidemia, n (%)	5	(25%)	12	(63.2%)	10	(50%)	0.051
Previous PCI, n (%)	1	(5%)	5	(26.3%)	4	(20%)	0.188
Previous AMI (last 3 months), n (%)	2	(10%)	4	(21.1%)	3	(15%)	0.631
COPD, n (%)	2	(10%)	0	(0%)	3	(15%)	0.233

Categorical variables shown as n (%); continuous variables shown as mean ± standard deviation (minimum–maximum).

AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MECC, miniaturized extracorporeal circulation; OPCABG, off-pump coronary artery bypass grafting; PCI, percutaneous coronary intervention; SECC, standard extracorporeal circulation.

These data suggest us that cardioplegic myocardial protection was equally effective in both MECC and SECC groups. The off-pump technique leads to a lower myocardial damage during the operation, but no differences can be detected during postoperative days.

Inflammatory Response

Systemic and cardiac IL-6 levels showed a constant rise during and after cardiac surgery in all groups with no significant differences among them.

Tumor necrosis factor-α arterial levels were comparable before surgery in every group, but they significantly increased during CPB in SECC group, peaking at the end of the operation with a statistical difference at time T4 (**Figure 2A**). During postoperative days those differences disappeared. The trend suggests an important intraoperative systemic release of TNF-α in SECC group but no postoperative differences according to the short life of this molecule. A cardiac release of TNF-α was observed mainly in SECC group. We experienced an important variation in cardiac TNF-α values leading to high standard deviations and no statistical significance of the differences between SECC group and other patients.

Arterial E-selectin levels showed a constant significant decrease during and after operation (**Figure 2B**) in every group. We noticed the same trend with a significant effect of time but no effect of different treatments in all groups. This suggests a constant consumption of soluble E-selectin due to the effect of surgical approach. Cardiac release of E-selectin did not show any statistical difference among the groups.

Monocyte chemotactic protein-1 arterial levels showed a significant increase in SECC patients after removing the aortic clamp (**Figure 2C**). In this group, MCP-1 arterial levels remained high until the end of the operation and went back to lower values after 24 hours. Cardiac MCP-1 levels showed a significant increase in SECC group patients at time T2 and T3 (**Figure 2D**). These data suggest higher systemic and cardiac MCP-1 release during CPB with the standard system.

Table 2. Intraoperative Data

Variables	SECC (n = 20)		MECC (n = 19)		OPCABG (n = 20)		*p*
No. of distal anastomoses	2.7 ± 0.5	(2–3)	2.8 ± 0.5	(2–4)	2.7 ± 0.5	(2–3)	0.050
BIMA	2	(10%)	5	(26.3%)	2	(10%)	0.265
TAMR	1	(5%)	2	(10.5%)	3	(15%)	0.577
Complete revascularization, n (%)	16	(80%)	18	(94.75%)	13	(65%)	0.070
CPB time (min)	94.3 ± 18.8	(65–134)	92.5 ± 27.8	(54–153)			0.821
Aortic cross-clamping time (min)	73.3 ± 16.2	(45–101)	71.4 ± 20.8	(45–113)			0.754
Lowest Ht (%)	23.8 ± 3.3	(18.6–30.8)	25.5 ± 3.6	(18.5–30.8)			0.121
Highest Ht (%)	26.9 ± 3.9	(20.7–36.7)	28.4 ± 2.9	(24.1–33.6)			0.190
Lowest ACT (sec)	466.5 ± 82.0	(356–716)	350.7 ± 51.8	(290–462)			<0.001
Highest ACT (sec)	556.6 ± 110.6	(449–863)	469.2 ± 263.6	(305–1,500)			0.181
Cell saver blood (ml)	406.1 ± 129.5	(200–700)	476.8 ± 166.7	(150–860)	210 ± 104.6	(50–380)	<0.001

Categorical variables shown as n (%); continuous variables shown as mean ± standard deviation (minimum–maximum).

ACT, activated clotting time; BIMA, bilateral internal mammary artery; CPB, cardiopulmonary bypass; Ht, hematocrit; MECC, miniaturized extracorporeal circulation; OPCABG, off-pump coronary artery bypass grafting; SECC, standard extracorporeal circulation; TAMR, total arterial myocardial revascularization.

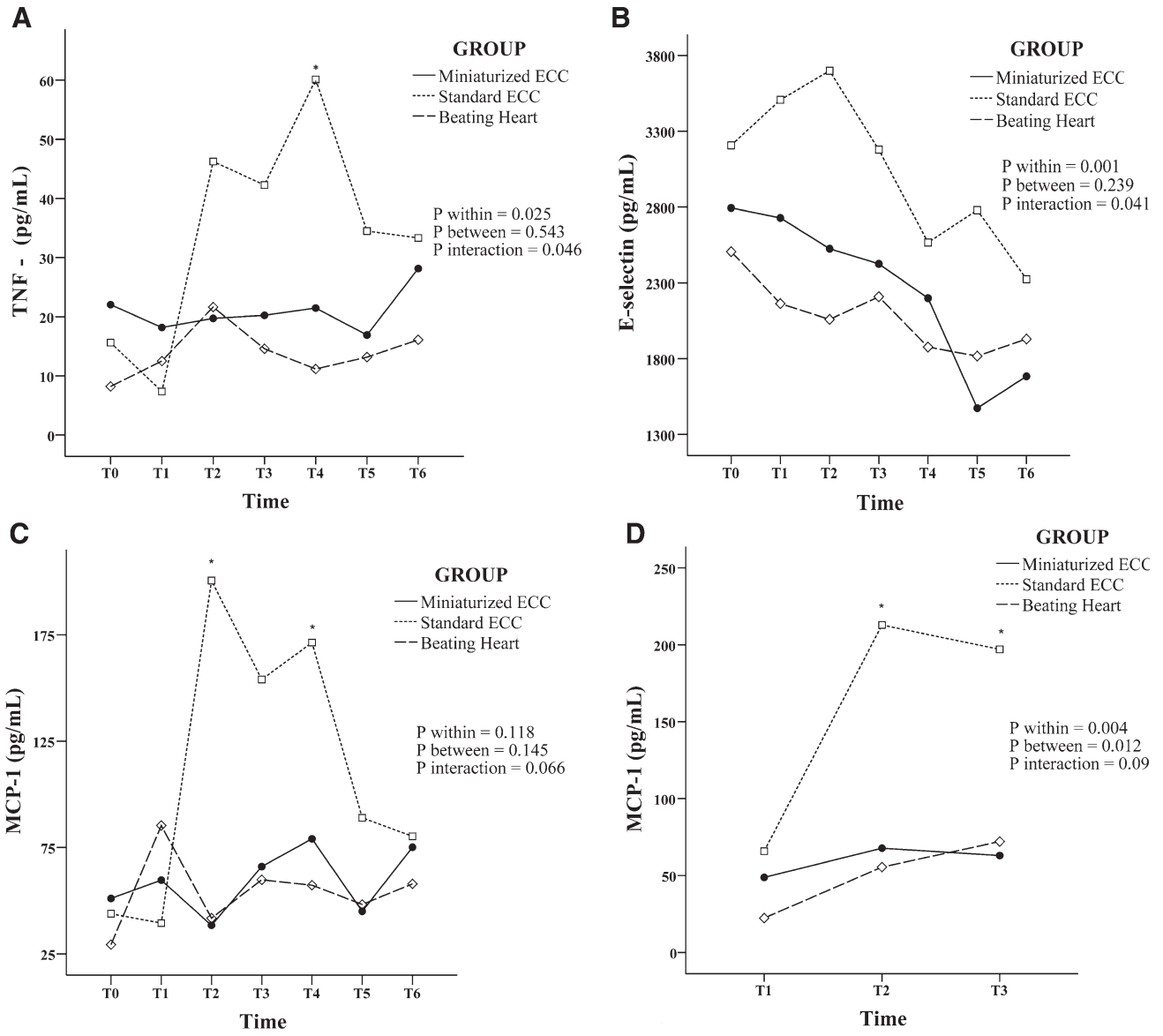

Figure 2. A: Time trend of systemic tumor necrosis factor (TNF)-α levels in patients undergoing miniaturized extracorporeal circulation (MECC), standard extracorporeal circulation (SECC), or off-pump coronary artery bypass grafting (OPCABG). **B**: Time trend of systemic E-selectin levels in patients undergoing MECC, SECC, or OPCABG. **C**: Time trend of systemic monocyte chemotactic protein (MCP)-1 levels in patients undergoing MECC, SECC, or OPCABG. **D**: Time trend of cardiac MCP-1 levels in patients undergoing MECC, SECC, or OPCABG; blood samples from coronary sinus. ECC, extracorporeal circulation; T0, before the induction of anesthesia; T1, before cardiopulmonary bypass (CPB) start or before the first distal anastomosis in OPCABG group; T2, 5 minutes after aortic clamp removal or after the last distal anastomosis in the OPCABG group; T3, 5 minutes after weaning off CPB or 15 minutes after the last distal anastomosis in the OPCABG group; T4, at the end of operation; T5, 24 hours after operation; T6, 48 hours after operation.

Hemodilution and Coagulation

All patients presented comparable values of hemoglobin before operation. OPCABG patients showed the highest hematocrit and hemoglobin values at T2 and T3, whereas SECC and MECC groups showed a decrease after CPB start as expected. Hematocrit levels increased significantly at the end of surgical procedure in SECC and MECC groups and reached the same values as OPCABG group (SECC 29.9±3.2%; MECC 28.9±3.8%; OPCABG 30.2±3.2%). The same trend was observed in cardiac sinus values. Despite those results, a statistical difference was observed at first postoperative day with higher values in MECC patients (SECC 32.2±3.3%; MECC 33.7±2.0%; OPCABG 30.8±3.2%; $p = 0.01$).

No differences were observed in platelets and fibrinogen serum values. D-dimer levels were comparable in every groups before surgery; they increased at the end of the operation with higher values in OPCABG group but with no statistical significance.

Postoperative bleeding, PRC, platelet units, and fresh frozen plasma transfusions were similar in every group (**Table 3**).

Discussion

In our prospective randomized trial, we found no differences in early clinical outcome in low-risk patients undergoing CABG with MECC, SECC, or OPCABG. We noticed several differences in biochemical inflammatory patterns, and we

Table 3. Postoperative Data

Variables	SECC (n = 20)		MECC (n = 19)		OPCABG (n = 20)		*p*
Intubation time (h)	11 ± 2	(8–15)	11.6 ± 3.7	(8–24)	13.3 ± 6.3	(8–26)	0.227
Total bleeding (ml)	363.5 ± 188.8	(70–800)	422.9 ± 268.6	(90–1,260)	431.4 ± 243.9	(160–1,050)	0.080
ICU stay (h)	27.2 ± 9.7	(18–48)	27.9 ± 111.7	(15–60)	33.2 ± 10.8	(19–48)	0.166
Patients requiring inotropes, n (%)	4	(20%)	6	(31.6%)	11	(55%)	0.063
Atrial fibrillation	7	(35%)	7	(36.8%)	7	(35%)	0.992
Patients receiving transfusion during hospitalization, n	7	(36.8%)	8	(40%)	10	(50%)	0.684
Number of packed red cells required during hospitalization, n	1.9 ± 0.7	(1–3)	2.6 ± 1.1	(1–4)	2.0 ± 0.7	(1–3)	0.270
Postoperative hospital stay (d)	5 ± 1.4	(3–8)	4.7 ± 1.2	(3–7)	5.3 ± 1.4	(3–10)	0.496

Categorical variables shown as n (%); continuous variables shown as mean ± standard deviation (minimum–maximum).
SECC, standard extracorporeal circulation; MECC, miniaturized extracorporeal circulation; OPCABG, off-pump coronary artery bypass grafting; ICU, intensive care unit.

focused on myocardial ischemia and systemic endothelial activation. The analysis of the results shows that MECC induces a lower TNF-α and MCP-1 activation in comparison with SECC, and it might be considered as equal as OPCABG.

Many authors demonstrated the superiority of MECC compared with standard CPB in terms of reduced postoperative arrhythmias, blood loss and transfusion burden,[2] endothelial and myocardium damage,[4] better liver function, reduced oxidative stress,[5] pulmonary damage,[5] lower C-reactive protein levels,[6] lower monocyte activation, IL-6 and TNF-α release,[3] and reduced coagulation activation.[10] Harling *et al*.[11] showed no significant differences between MECC and OPCABG patients concerning clinical outcomes suggesting MECC as an effective and safe alternative to OPCABG. The results of our trial confirmed no significant clinical differences among groups in terms of mortality and morbidity in a population with low preoperative risk. In literature, MECC is widely applied in low-risk populations with a few clinical benefits.[5] Otherwise, a better knowledge of the molecular pathways causing CPB-related inflammation might be valuable for the improvement of the clinical management of high-risk patients in cardiac surgery.

Interleukin-6, TNF-α, and MCP-1 are the main proinflammatory cytokines in acute inflammatory response during and after CPB. IL-6 increases in major surgeries 2–4 hours after skin incision,[12] and it is also triggered by CPB.[3,13] We observed no significant differences in systemic and cardiac IL-6 release among groups. Many authors found no significant differences in IL-6 release among MECC and other perfusion and surgical techniques.[14] On the other hand, Immer *et al*.[15] and Fromes *et al*.[3] showed lower IL-6 values in MECC patients. Although IL-6 cytokine is a well-known marker of inflammatory response, it is affected by many variables coming from a complex interaction of surgical trauma, extracorporeal circulation, drug effects, and genetic substrate. Therefore, IL-6 is not useful to demonstrate the efficacy of MECC in reducing inflammatory response rather than underline that the surgical trauma is the main cause of IL-6 release in low-risk patients.

Myocardium is a source of TNF-α in response to ischemia/reperfusion damage. We observed a significant intraoperative increase of TNF-α systemic and myocardial values in SECC group. On the other hand, myocardial protection was equally effective in both MECC and SECC groups as demonstrated by troponin-T and CK-MB release. So far, plasma levels of TNF-α might not be related to the CPB circuit used during surgery as previously demonstrated by Fromes *et al*.[3] Therefore, we hypothesize that CABG with MECC is associated with an equivalent release of TNF-α compared with off-pump surgery. Murakami *et al*.[16] confirmed such an hypothesis through the test of soluble TNF receptors.

Leukocyte adhesion and endothelial cell activation are important processes related to post-CPB morbidity and mortality.[17]

E-selectin is exclusively expressed by the cytokine-activated endothelial cells, and its soluble form increases in patients affected by cancer, hematological disorders, ischemic heart disease, atherosclerosis, hypertension, diabetes, and septic shock.[18] Because TNF-α increases during SECC and induces the E-selectin synthesis, we expected an increase of systemic and myocardial E-selectin levels, especially in SECC group. Our study showed a decrease of E-selectin levels during and after surgery without any difference among the groups. Similar results were noticed by Panagiotopoulos *et al*.[19] Other previous studies found a decrease in soluble E-selectin during CPB,[20] and some others noticed stable values or postoperative increase at 12, 24,[21] or 48 hours[22] after CPB. Those data might be explained considering that soluble E-selectin competes with membrane E-selectin for their shared leukocyte ligands, showing an inhibitory function hence in leukocyte recruitment.[20] Moreover, other studies failed to demonstrate the superiority of a CPB technique over another one, as far as E-selectin levels.[23] This kind of evidences suggest that surgical trauma and cardiovascular disease have a pivotal role in the control of E-selectin–related inflammatory pattern.

Activated endothelium also releases MCP-1. Monocyte chemotactic protein-1 induces an increase of brain endothelial permeability, it facilitates the HIV-viral spread within the central nervous system, and it was recognized as an angiogenetic chemokine. Monocyte chemotactic protein-1 is also involved in the progressive diabetic nephropathy as well as in inflammatory renal diseases,[24] and, at last, it is responsible for the recruitment of monocytes in the infarcted myocardium in the first 5 hours after reperfusion.[8] We demonstrated higher systemic and cardiac MCP-1 levels in SECC group during CPB and a successive decrease 24 hours after surgery, suggesting a relevant role of CPB in the upregulation of this kind of chemokine and a protective role of MECC. Ghorbel *et al*.[25] confirmed

an upregulation of MCP-1 gene and protein expression during standard CPB compared with OPCABG. If we consider the role of MCP-1 in several pathophysiological conditions, our data might suggest the use of MECC in high-risk patients such as patients with renal impairment, central nervous system damage, HIV infection, diabetes, and recent myocardial ischemia. In case of such an ischemia, MCP-1 contributes to the control of the angiogenic remodeling process in the heart subjected to cardioplegic arrest.

In conclusion, we demonstrated that MECC might be an effective alternative to SECC and reduces inflammation markers levels to values comparable with OPCABG. Therefore, MECC might be recommended in high-risk patients.

Limitations

The main limitation of our study is its small sample size. It is due to the single-centre study design that was chosen in order to guarantee uniformity in perioperative management. We enrolled a selected population so to minimize bias. Because we are not able to extend our considerations over high-risk patients, more randomized studies are mandatory to confirm the role of MECC in high-risk patients as well. Furthermore, we do not have any data about mid- and long-term follow-up, and we might also miss some differences in the late postoperative course.

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