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Mini Extracorporeal circulation minimizes coagulation abnormalities and ameliorates pulmonary outcome in coronary artery bypass grafting surgery.

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ABSTRACT

Hemostasis is impaired during CABG and coagulation abnormalities often result in clinically relevant organ dysfunctions, eventually increasing morbidity and mortality rate. Fifteen consecutive patients with coronary artery disease submitted to conventional EEC (ECC) have been compared with 15 matched patients using mini-ECC (MECC). Postoperative lung function was evaluated according to gas exchange, intubation time and lung injury score.

Thrombin-antithrombin complex levels, prothrombin fragments formation and thromboelastography clotting times were lower in MECC group (p=0.002 and p<0.001, respectively) whereas postoperative blood loss was higher in ECC group (p=0.030) and more patients required blood transfusion (p=0.020). In MECC group postoperative gas exchange values were better, intubation time shorter and lung injury score lower (p<0.001 for all comparisons).

Our study suggests that the MECC induces less coagulation disorders leading to a lesser postoperative blood loss and a better postoperative lung function. This approach may result particularly advantageous in high-risk patients.

INTRODUCTION

Despite the improvement in extracorporeal circulation (ECC) and the routinary intraoperative administration of anti-inflammatory and anti-fibrinolytic drugs (three phosphodiesterase type III inhibitors and/or tranexamic acid), a remarkable activation of coagulation, revealed by elevated levels of prothrombin fragment 1-2 (PF1+2), thrombin-antithrombin complex (TaTc) and inflammatory cytokines was detected after coronary artery bypass graft (CABG).[1-3] Such modifications may lead to postoperative coagulopathy resulting in excessive bleeding and various levels of organ dysfunction.[4-8] During the last decade, a minimal extracorporeal circulation (MECC) has been proposed for CABG and valve surgery.[9-11] Circuit is smaller, less priming is required and, as a closed system with no reservoir and field suctions, air/blood contact is avoided. Indeed, several investigators have demonstrated better postoperative outcome in terms of reduced inflammatory response and postoperative blood loss.[12-14] However, for our knowledge, there are no studies that include PF1+2, TaTc formation and clotting evaluation by thromboelastography (TEG). The aim of this study was to evaluate the impact of either conventional ECC or MECC in terms of coagulation disorders, blood loss and early postoperative lung function in patients undergoing CABG.

MATERIALS AND METHODS

Fifteen consecutive patients with coronary artery disease underwent conventional EEC were compared with 15 matched patients undergoing MECC. Exclusion criteria included reoperation, associated cardiac pathologies requiring combined procedure or patients with carotid artery disease requiring surgical or percutaneous intervention. Mean age was 68.5 ±8.2 years. Preoperative data are summarized in table 1. Approval for this study was obtained from the institutional review board. Informed consent was obtained from patients in accordance with the declaration of Helsinki.

Coagulation and fibrinolysis analysis

To evaluate coagulation and fibrinolysis changes during cardiopulmonary bypass (CPB) time, TaTc and PF1+2 formation were analyzed by immune-enzymes laboratory procedures (Dade-Behring GmbH, Schwalbach, Germany). For this purpose, blood samples were taken from the radial artery pre, intra and postoperatively (T0= preoperatively; T1= sternotomy, T2-T5= beginning, 15, 30 and 45 minutes of CPB time respectively; T6= after protamine administration and T7= 3 hours after surgery). To evaluate clot formation, the thromboelastography analyzer (TEG 5000 - Haemoscope, Niles, IL) was used: a sample (1 ml) of unanticoagulated blood was activated with Kaolin, and then 0,36 ml of this kaolin-activated blood was pipetted into the cup. When blood samples were taken during CPB, a heparinase cup was used, to counteract heparin effects. A characteristic tracing is produced from which the main parameters are measured, R time, K time, alpha angle, and maximum amplitude (MA). The R value (in millimeters), measured from the beginning of the tracing until amplitude of 2 mm is reached, represents the time necessary for initial clot formation (normal range values are 4-8 min). The K value (in millimeters) is the time interval from the end of the R value until an amplitude of 20 mm is attained and appraises the rapidity of fibrin build-up and cross-

linking as the clot forms (normal range values are 0-4 min). The alpha-angle value

similarly assesses the kinetics of clot development and it is measured as the slope of the

outside divergence of the tracing from the point of the end of the R-value, and reflects the

function of both fibrinogen and platelets. The MA value is a reflection of the maximum

strength of the fibrin clot and is influenced most importantly by fibrinogen levels, platelet

numbers, and platelet function as well as by factors VIII and XIII (normal range values 54-

72 mm). The LY30 parameter measures percent lysis at 30 minutes after MA is

reached.[15]

Pulmonary evaluation

To evaluate pulmonary function, PO_2, PCO_2, tension-inspired oxygen fraction ratio (PaO_2-

FIO_2), alveolar-arterial oxygen difference (A-a DO_2) were recorded; Blood samples were

taken from the radial artery at different times as follows: T0= preoperatively before

intubation T1 and T2= at end and 3 hours after surgery; T3= patient in spontaneous

ventilation in T tube with 50% FiO_2, T4= one hour after extubation with oxygen mask

support (50%), and T5= 24 hours after extubation. Chest X-Rays were taken

preoperatively, after arrival to the intensive care unit (ICU) and in first and second

postoperative day and were evaluated by two independent radiologists blinded to the

study for degree of atelectasis. An established atelectasis scoring system was used as

follows: 0 = no alveolar consolidation; 1 = alveolar consolidation confined to 1 quadrant; 2

= alveolar consolidation confined to 2 quadrant; 3 = alveolar consolidation confined to 3

quadrant; 4 = alveolar consolidation confined to 4 quadrant.[16] The lung injury score (LIS)

was calculated from the number of quadrant on the chest radiograph with opacities and

the PaO2-FIO2 ratio.[16] The LIS ranges between 0 (no injury) to 4, with values above 2.5

indicative of acute respiratory distress syndrome (ARDS) and between 0 and 2.5 of acute

lung injury (ALI).[17]

Intraoperative management

Preoperatively, all patients were premedicated with morphine (10 mg i.m.) and

scopolamine bromhydrate (0,25 mg i.m.). On arrival in the operating room, all patients

underwent general anaesthesia induction with Fentanyl (5γ/Kg) and Midazolam (0.1-0.2

mg/Kg) and maintenance with Sevoflurane (1 MAC) and remifentanyl (0,15-0,25γ/kg).

Neuromuscolar blockade was obtained by Cisatracurio Besylate (0.2 mg/Kg). After

midline sternotomy and internal thoracic artery harvesting, heparin was given to achieve

activated clotting time (ACT) target of at least 420 seconds. Cardiopulmonary bypass was

instituted via ascending aorta cannulation (24Fr) and a two-stage venous cannula in the

right atrium (34/46 and 32/40Fr in group 1 and 2, respectively). In the MECC group the

venous cannulation is secured by a second snare around the atrial incision to ensure

stabilization of the cannula and avoid air aspiration into the system, de airing of the

venous line is mandatory. During ECC time, active drainage is applied (up to -40mmHg) if

required. Venting was accomplished by using a needle in the ascending aorta, which

was connected through a drop chamber to the venous line (MECC group) or to the

reservoir (ECC group). In all patients, average blood flow rate was 2.5 L/min/ m2 with

systolic pressure ranging between 60 and 80mm Hg, and esophageal temperature was

maintained between 34°C and 36°C. Myocardial arrest and protection during cross-clamp

time was achieved by infusion of intermittent anterograde hyperkalemic warm blood

cardioplegia repeated every 20 minutes. In none of the groups reservoir suction was

used and blood loss from the surgical field was collected and processed by a cell saving

device (Electa Concept Dideco-Sorin, Sorin Biomedica, Mirandola, Modena, Italy) and re-

transfused at the end of surgery.

Conventional extracorporeal circuit (ECC group)

The conventional ECC circuit was composed by a roller pump (Stockert-Sorin S5, Sorin

Biomedica, Mirandola, Modena, Italy) and by a membrane oxigenator with an

incorporated cardiotomy reservoir (Sorin Synthesis, Sorin Biomedica, Mirandola,

Modena, Italy). Priming was achieved by 1473,1 ± 319,2 ml of Ringer acetate, Voluven

and Mannitol 18% (40%, 40% and 20% of volume, respectively).

Mini extracorporeal circuit (MECC group)

The MECC system consists of a closed system composed of a centrifugal pump (Maquet

Rotaflow; Hirrlingen, Germany) and membrane oxigenator (Maquet Quadrox D;

Hirrlingen, Germany). The venous line was directly connected to a centrifugal pump for

active drainage. Priming was achieved with mean volume of vs. 873,1 ± 139,4 ml (ringer

acetate, voluven and mannitol 18% with the same proportions described before).

Postoperative management

At the end of surgery patients were transferred to the intensive care unit and received

propofol IV of 0.5-5 mg/Kg/h to achieve Ramsey sedation score 2-3 until body

temperature reached 36°C. Propofol infusion was discontinued after verifying

hemodynamic stability and chest drains lower then 100 ml/h for at least 2 hours.

Extubation criteria included pH between 7,37-7,42, respiratory rate ≤ 12 and tidal volume

≥ 8 ml/kg, PaO_2 values >100 mmHg with FiO_2≤ 0,5 and SO_2 98-100%.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov 1-

sample test and are reported as mean ± SD. Variables with a skewed distribution were

expressed as medians and interquartile range. The unpaired Student's t-test and Mann

Whitney U-test were used to compare continuous variables between groups. Gas

exchange values, PF 1+2, TaTc, lactate and haemoglobin were compared by repeated

measures analysis of variance (ANOVA). Categorical variables are expressed as

proportion and percentages. Differences in nominal values were analyzed by using the

chi-square test. P values less than 0.05 were considered statistically significant. Data

were analyzed using Statview 8.0 (SAS Institute Inc, Cary NC).

RESULTS

Even if no formal randomization was performed, as depicted in Table 1, all preoperative

variables evaluated in this study were matched in both groups with the exception of a

higher incidence of 3 artery coronary disease and diabetes in MECC group (p=0.05 and

0.04, respectively). Furthermore, age was also slightly higher in MECC group (p=NS). No

hospital death or major postoperative complications occurred in either of the patient

groups and there were no differences in postoperative ICU and hospital stays. As

expected, circuit priming was significantly higher in ECC group (1473,1 ± 319,2 vs. 873,1

± 139,4 ml. p<0.001). Mean distal and proximal anastomosis were 3±0,9 and 1,7±0,6 in

group 1 and 3,1±0,7 and 1,5±0,7 in MECC group (p=NS), respectively. Cardiopulmonary

bypass time and cross clamp time were 86,3±22,3 vs. 83,2±19,2 and 46,2±13,8 vs.

46,2±14,2 in group 1 and 2 (p=NS), respectively. Although ACT target, cross clamp and

extracorporeal circulation times were similar in both groups, the total heparin

administrated was significantly higher in ECC group (26,961 ± 6,634 vs. 18,888 ± 4,672

UI/pt, p=0.001).

Coagulation and fibrinolysis analysis

Both TaTc and PF1+2 formation were lower in MECC group at all intraoperative

timepoints, as well as 3 hours after the end of surgery (Fig 1). Also rotation

thromboelastography analysis revealed shorter R and K values (table 2) in MECC group,

suggesting earlier clot stabilization. As a consequence, blood loss in MECC group was

significantly lower in first postoperative day (223.1±64.1 ml vs. 419.6±310.9 ml, p=0.030)

and fewer patients were transfused (1 pt. vs 7 pts, *p* =0.020).

Lung function evaluation

Postoperative Pa-FIO2 ratio compared to preoperative values was significantly worse in

ECC group (330.5±63.9 mmHg vs. 215.8±48.9 mmHg, *p*= 0.001) as compared to MECC

group (286.5$\pm$49.9 mmHg vs. 278.7$\pm$76.5 mmHg, *p*=NS). In both groups postoperative A-a DO$_2$, in comparison to preoperative, was significantly decreased (Table 3). At the time of extubation, arterial blood gas values were similar in both groups, however to achieve the extubation criteria, patients in ECC group were intubated for a longer time (range 5-17 vs. 4-9 hours, p=0.040). Arterial blood gas sample data and comparison between the conventional ECC and MECC for postoperative pulmonary function are reported in table 4. Based on postoperative chest X-Rays and gas values, lung injury score found to be significantly higher in ECC group in the first postoperative day (1.5$\pm$0.6 vs. 0.9$\pm$0.5, p=0.010).

DISCUSSION

Despite the benefits of MECC in comparison with the conventional ECC in terms of residual inflammatory response have been already reported,[9,10,13] there is a paucity of functional coagulation studies. To answer to this question, we analysed, in two groups of comparable patients submitted to EEC (15) or MECC (15), the level of hemostasis activation and its possible correlation with transfusional need and lung postoperative morbidity. In two separate reports, less thrombin (TaTc, PF1+2) and Plasmin-Antiplasmin complex formation have been reported, but no clinical benefits in terms of less blood transfusion and reoperation for bleeding has been demonstrated.[11,12] In our study, in addition to the reduction of TaTc and PF1+2 formation, the impact of MECC on the haemocoagulative system was also demonstrated by TEG, where R, K and MA values indicated a better clot stability. The effect of the better systemic coagulation homeostasis in MECC group also leaded to lower blood loss during the first postoperative day (p=0.030) and fewer blood transfusions (p=0.030).

A second important advantage resulting from the use of MECC is the reduction of pulmonary dysfunction, a frequent complication in the early postoperative period that might vary from silent clinical manifestation to severe respiratory insufficiency and ARDS, requiring prolonged mechanical ventilation, facilitating superimposed infection. This risk can be enhanced especially in elderly patients with history of chronic obstructive pulmonary disease[18] and in patient receiving a conspicuous red blood cells transfusional load.[19] The physiopathology of lung injury after cardiac surgery is still matter of debate with some authors emphasizing the role of direct contact of blood with the synthetic surface of the CPB circuit inducing inflammatory cytokines production and causing activation of endothelial cells and adhesion of complement-activated neutrophils leading to tissue injury mediated by oxygen-derived free radicals.[20,21]

A further hypothesis contemplates an association between blood transfusion and
pulmonary complications in cardiac surgery, leading in some cases to a higher incidence
of transfusion related lung injury (TRALI). Both the amount of red blood cell products and
the level of bioactive lipids or the presence of histocompatibility leukocyte antigens or
leukocyte agglutinating antibodies in the transfused products have been associated with
increased pulmonary capillary permeability and increased pulmonary vascular
leakage.[19,22] In our study, the reduction of transfusional support in the MECC group might
have contributed to the better postoperative gas exchange and, correspondingly, to a
better lung injury score and a shorter mechanical ventilation time. High risk patients
and/or those undergoing cardiac surgery after an unsuccessful attempt of angioplasty,
that received intense double antiaggregation therapy determining a marked increase in
blood loss, transfusion requirements and reopening for bleeding may especially benefit
from the minimization of coagulation abnormalities.[23-27]

In conclusion, our study suggests that the use of MECC systems may reduce coagulation
abnormalities and guarantee better postoperative outcome in terms of reduced blood
transfusion need and better lung function as compared to patients undergoing
conventional ECC.

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Table 1 Preoperative variables

Variables	Group ECC (15 pts)	Group MECC (15 pts)	p
Age (years)	65 ± 8	72,1 ± 8	ns
Male sex (n)	14 (94%)	10 (66%)	ns
Hypertension (n)	12 (76%)	13 (84%)	ns
Diabetes Mellitus (n)	3 (20%)	9 (60%)	0,04
Smoke (n)	3 (20%)	3 (20%)	ns
Body surface (m^2)	19,2 ± 1,4	19,2 ± 4,6	ns
COPD (n)	5 (30%)	6 (38%)	ns
Atrial fibrillation (n)	0	1 (3%)	ns
Peripheral vasculopaty (n)	1 (6%)	5 (30%)	ns
Coronary artery disease (n)			
One vessel	1 (6%)	0	ns
Two vessels	2 (14%)	0	ns
Three vessels	11 (76%)	15 (100%)	0,05
Unstable Angina (n)	1 (6%)	5 (30%)	ns
NYHA III-IV	3 (20%)	5 (30%)	ns

Table 2. Thromboelastography variables (Timing for evaluation T0-T7 are reported in materials and methods)

Variables	*T0*	*T1*	*T2*	*T3*	*T4*	*T5*	*T6*	*T7*
R (min)†								
ECC	9,0±2,2	10,2±3,2	17,2±12,4	15,8±5*	11,6±3*	11,9±3,8**	8,3±4,1	9,1±2,1
MECC	11,1±3,9	11,2±3,8	11,7±3	11,5±3,2	9,4±1,6	8,2±1,3	7,3±1,1	7,8±2,5
K (min)††								
ECC	2,3±0,1	2,9±0,9	5,4±3,8**	4,4±1,3***	4,0±1,2*	3,2±0,7**	3,2±1,1	2,9±1
MECC	3,6±1,9	3,7±1,2	2,3±0,6	2,4±0,8	2,2±1,1	2,0±1,2	3,1±1,8	2,6±0,9
MA (mm)								
ECC	72,5±5	67,9±3,7	58,2±8,0	61,8±5,9	60,3±4	63,3±3,1	64,9±3,9	66±5,4
MECC	68,4±8,8	61,4±13,8	60,9±6	57,2±14,4	61,4±6,5	65,1±7,8	65±6,9	68,9±5,4

† ANOVA $p < 0,001$

†† ANOVA $p < 0,0001$

* $p < 0,05$

** $p < 0,01$

*** $p < 0,001$

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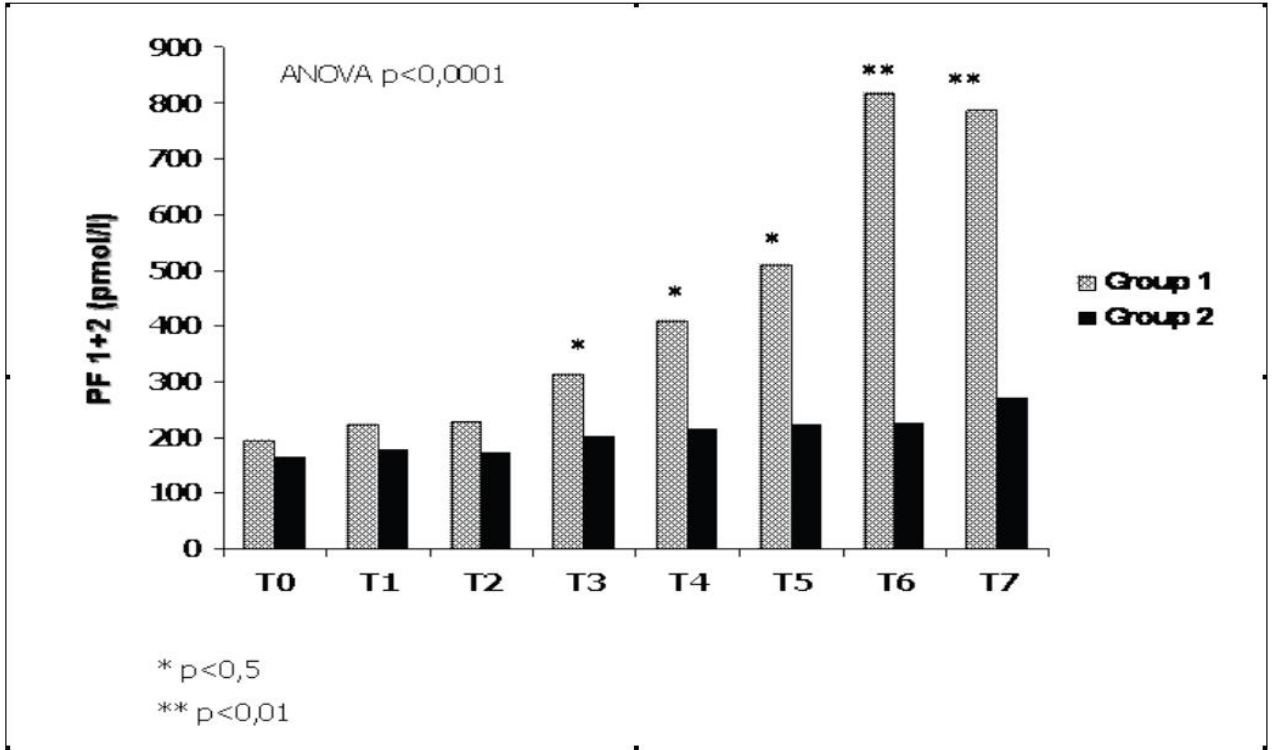34
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Table 3. Pulmonary function variables. (Timing for evaluation T0-T5 are reported in materials and methods)

Variables *	ECC Group	MECC Group	p
PaO_2-FIO_2 ratio (mmHg)†			
(T 0)	330,5±63,9	286,5±49,9	NS
(T 1)	308,4±100,5	419,0±80,4	0,007
(T 2)	274,9±67,0	366,4±78,7	0,005
(T 3)	302,9±93,6	321,4±56,3	NS
(T 4)	196,8±80,1	270,6±75,3	0,03
(T 5)	215,8±48,9	278,7±76,5	0,02
A-a DO_2 (mmHg)††			
(T 0)	42,5±24,3	53,0±24,4	NS
(T 1)	331,2±88,5	230,1±69,7	0,005
(T 2)	272,7±120,5	167,6±59,4	0,01
(T 3)	164,8±32,6	144,9±27,7	NS
(T 4)	261,3±152,1	172,1±48,8	NS
(T 5)	200,1±28,4	141,5±49,3	0,001
Lung injury score (n)†††			
Postoperative day 0	0,7±0,1	0,5±0,3	NS
Postoperative day 1	1,5±0,6	0,9±0,5	0,01

† ANOVA   p<0,01
†† ANOVA   p<0,0001
††† ANOVA p<0,05

LEGEND TO FIGURE 1

Figure 1. Prothrombin fragments (PF1+2) values (A) and Thrombin–antithrombin complex

(TATc) values (B) in group 1 (ECC) and group 2 (MECC). (Timing for evaluation T0-T7 are

reported in materials and methods section)

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FIGURE 1

A

B