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The use of Minimized Extracorporeal Circulation System has a Beneficial Effect on Hemostasis—A Randomized Clinical Study

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ABSTRACT

Background. Conventional cardiopulmonary bypass (CPB) is associated with increased coagulation and fibrinolytic activity. A closed miniaturized bypass circuit (CorX) features a significantly reduced tubing set, an integrated pump, and an air removal system without a cardiotomy reservoir. In a prospective randomized trial, the effects on hemostasis were investigated while comparing CorX with conventional CPB in patients undergoing coronary artery bypass grafting.

Methods. Over a period of 1 year, 81 patients were randomly assigned either to the CorX system (n = 39, group A) or standard CPB system (n = 42, group B). Primary end-points were platelet count, plasmin-antiplasmin complex (PAP), prothrombin fragments 1+2 (F1+F2), D-dimers, and fibrinogen. Secondary end-points were hematocrit, blood loss in the first 12 hours postoperatively, transfused packed red blood cells, and fresh frozen plasma in the first 24 hours postoperatively. In addition, we analyzed partial thromboplastin time, prothrombin time, and antithrombin III.

Results. After aortic declamping, PAP complex and prothrombin F1+F2 were significantly lower in group A than in group B. The difference in D-dimers between groups reached significance at 1 hour post-CPB. Hematocrit values at the end of CPB measured 26 ± 6% in group A versus 22 ± 4% in group B (P = .01). The rest of the observed parameters did not significantly differ between groups.

Conclusion. Postoperative blood loss was not reduced in the present study. However, the use of the CorX system leads to a significant suppression of activation of coagulation and fibrinolytic cascades compared to conventional CPB, suggesting that miniaturized extracorporeal circuits are a step forward toward reduced imbalance of hemostasis in cardiac surgery.

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INTRODUCTION

Cardiopulmonary bypass (CPB) is still a mandatory tool for the vast majority of adult and pediatric cardiac operations. The employment of CPB is associated with several drawbacks, among which the activation of the coagulation and fibrinolytic systems, leading to increased risk of perioperative bleeding and thrombosis, are important factors [Kirklin 1983; Westaby 1987]. Amelioration of these CPB-induced damaging effects has been the aim of many research groups. Because postoperative imbalance of hemostasis is a multifactorial process, several strategies have been attempted to reduce the invasiveness of CPB. These include potentially increased biocompatibility of perfusion circuits [Gu 1993; Daniel 1996; Muehrcke 1996; Wimmer-Greinecker 1999; Gourlay 2001], modified ultrafiltration [Naik 1991; Luciani 2001], leukocyte filtration [Matheis 2001; Scholz 2002], the application of complement inhibitors [Chai 2000], the use of glucocorticoids [Hill 1994; Hill 1995], protease inhibitors [Murase 1993; Wachtfogel 1993], and others [Mou 2004].

A novel concept, the use of minimized extracorporeal circuits [von Seggesser 2003], has recently been suggested to reduce the impact of CPB, especially on hemostasis by means of markedly reduced perfusion circuit area and priming volume. The CorX system (CardioVention, Santa Clara, CA, USA) follows this concept and consists of a closed circuit with a lower priming volume and fewer lines, an integrated centrifugal pump, oxygenator, and air removal system. In addition, neither a cardiotomy reservoir nor pericardial suction is used to minimize blood-air contact.

The aim of the present investigation was to compare the CorX system to our standard extracorporeal circulation system in a prospective randomized trial. We hypothesized that the employment of CorX for CPB during coronary artery bypass grafting (CABG) would reduce the impact on coagulation and fibrinolytic systems as seen with conventional CPB systems.

MATERIALS AND METHODS

Between August 2002 and October 2003, 81 patients scheduled for elective CABG were prospectively enrolled in this study after giving written informed consent and were randomly assigned to either the CorX system (n = 39, group A) or standard CPB (n = 42, group B) as used in our institution. Patients undergoing reoperations, combined proce-

Figure 1. The CorX system (on left) and the conventional heart-lung machine (on right).

dures, or presenting cases of emergency were excluded from this study. The study protocol was reviewed and approved by the local ethical committee. This patient cohort was studied as a subgroup of a prospective randomized trial involving 204 patients [Abdel-Rahman 2005].

All procedures were performed through median sternotomy and had central cannulation for CPB. Prior to onset of CPB, every patient intravenously received 350 IU/kg of heparin. Anticoagulation was monitored by measuring activated clotting time (ACT), which was maintained >400 sec during CPB by administration of additional heparin if required. Antegrade warm blood cardioplegia was intermittently delivered in both groups. At the end of CPB, intravenous administration of protamine sulfate in a 1:1 ratio of the initial dose of heparin served to reverse its effects.

The concept of the CorX system is characterized by a single device which integrates the functions of oxygenation, blood pumping (centrifugal pump), and air elimination. Designed as a closed circuit (Figure 1) without an additional suction line or venous reservoir, the system consists of an uncoated arterio-venous loop with a total surface area of less than 1.4 m^2. Only 500 mL of Ringer solution with 5000 IU heparin (Roche Pharma, Basel, Switzerland) served as the priming volume. No arterial line filter was used. Blood from the surgical field was collected in a cell-saving device (CATS; Fresenius AG, Bad Homburg, Germany).

For standard CPB, a complete preconnected tubing set with membrane oxygenator (Quadrox with SafeLine coating), Quart arterial filter, and cardiotomy reservoir was used with a standard roller pump (Jostra AG, Hirrlingen, Germany). Priming volume consisted of Ringer solution (1000 mL), 500 mL of hetastarch 10% (Braun Melsungen AG, Melsungen, Germany), 250 mL of mannitol 20% (Serag-Wiessner KG, Naila, Germany), and 10000 IU heparin.

Primary end-points of this investigation were hemostatic parameters including platelet count, plasmin-antiplasmin (PAP) complex, prothrombin fragments 1+2 (F1+F2), D-dimers, and fibrinogen. Secondary end-points were clinical parameters including hematocrit, blood loss in the first 12 hours postoperatively, transfused packed red blood cells, and fresh frozen plasma in the first 24 hours postoperatively.

Platelet count was preoperatively assessed at 1, 6, and 24 hours post-CPB. The PAP complex (ELISA, Haemochrom Diagnostica, Essen, Germany) and prothrombin F1+F2 (ELISA, Dade-Behring, Liederbach, Germany) were preoperatively evaluated, following the removal of the aortic clamp and at 1 hour post-CPB. The evaluation of the blood levels of D-dimers (Vidas D-dimer Exclusion, bioMerieux, Marcy-

Table 1. Patient Demographics, Operative, and Postoperative Data

	Group A, n = 39	Group B, n = 42	*P*
Age, y	68.6 ± 7.7	66.9 ± 8.0	NS
Sex, M:F	28:11	36:6	
Canadian Cardiovascular Society class	2.2 ± 0.7	2.3 ± 0.7	NS
EuroSCORE*			
Low-risk (0-2)	20	23	
Medium-risk (3-5)	14	12	
High-risk (>6)	5	7	
Number of diseased vessels	2.8 ± 0.4	2.7 ± 0.4	NS
Number of distal bypass anastomoses	3.1 ± 0.8	3.2 ± 0.7	NS
Cardiopulmonary bypass time, min	77 ± 25	78 ± 21	NS
Aortic cross-clamp time, min	44 ± 14	47 ± 17	NS
Operating time, min	175 ± 39	173 ± 42	NS
Intensive Care Unit stay, h	16 ± 18	20 ± 22	NS
Hospital stay, d	10 ± 4	9 ± 2	NS

*European System for Cardiac Operative Risk Evaluation [Nashef 1999].

IÉtolie, France) and fibrinogen (STA Fibrinogen, Roche Diagnostics, Mannheim, Germany) were undertaken at the same time points as the platelet count.

In addition, routine hemostatic parameters such as partial thromboplastin time (PTT) (STA APTT, Roche Diagnostics, Mannheim, Germany), prothrombin time (PT) (STA PT, Roche Diagnostics), and antithrombin III (AT III) (Coamatic LR antithrombin, DiaPharma, West Chester, OH, USA) were assessed at the same time points as the platelet counts.

Data are presented as mean ± standard deviation. Analysis of variance repeated measures were carried out using the Wilcoxon rank sum test and Kruskal-Wallis test. A *P* value < .05 was considered statistically significant. Analyses were performed using the SAS software package (SAS Institute, Cary, NC, USA).

RESULTS

Patients' characteristics and perioperative data were similar for both groups, as shown in Table 1. In particular, CPB time and aortic cross-clamp time were not significantly different. There was no early mortality. Durations of intensive care unit and hospital stay were similar between groups. One patient in each group required re-exploration due to excessive bleeding. The patient in group A presented with a diffuse bleeding whereas the patient in group B had surgical cause for bleeding.

The perioperative course of platelet counts for both groups is presented in Figure 2, depicting a slight decrease in the early postoperative period without significant difference between groups. Following the removal of the aortic clamp, PAP complex (Figure 3A) and prothrombin F1+F2 (Figure 3B) were significantly lower in group A than in group B (560 ± 261 ng/mL versus 1406 ± 1139 ng/mL, *P* <.0001; 1649 ± 660 IU/L versus 2831 ± 625 IU/L, *P* <.0001, respectively). One hour following CPB discontinuation, these parameters returned to levels similar to preoperative ones.

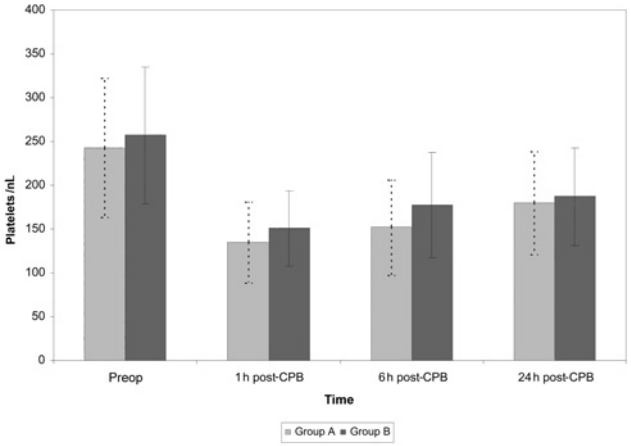

Figure 2. Perioperative values of platelets. Statistical significance was not reached at any time point.

The values for D-dimers (Figure 4A) were significantly higher in group B at 1 hour after CPB (0.6 ± 0.4 mg/mL versus 1.7 ± 1.1 mg/mL, *P* <.0001). In group A, D-dimers values increased slightly in the first 6 hours after CPB and reached nearly preoperative levels at 24 hours post-CPB, whereas these levels were still elevated in group B. Fibrinogen levels were similar in their perioperative course (Figure 4B) without statistical difference between group A and B; lowest values were seen 1 hour post-CPB, whereas maximum levels were reached 24 hours after CPB.

The effect of standard CPB on hemodilution was confirmed, as hematocrit values dropped from 31 ± 3% to 22 ± 4% in group B. However, the decrease was not so abrupt in the group A patients, as their values only lowered from 30 ± 2% to 26 ± 6%. The difference between the postoperative hematocrit values in both groups was found to be statistically significant (*P* = .01).

Regarding clinical parameters (Table 2), blood loss was not significantly different between groups in the first 12 hours postoperatively. During the first 24 postoperative hours, the amount of transfused fresh, frozen plasma, and packed red blood cells did not markedly differ either. Furthermore, routine coagulation parameters (PTT, PT, antithrombin III) did not show significantly different values between both groups (Table 3).

DISCUSSION

Cardiac surgery has only become possible with the advent of CPB a half century ago [Gibbon 1954]. For 50 years now, CPB has remained a mandatory tool for surgical treatment of the vast majority of pediatric and adult cardiac operations, contributing to a 12.9% increase of life expectancy in the United States [CDC 2004].

Despite its beneficial role, the use of CPB may result in some harm to the patient [Kirklin 1983; Westaby 1987]. The exposure of blood and blood elements at the nonendothelial surface of machine components results in a complex CPB-triggered proinflammatory and prothrombotic processes, potentially leading to temporary dysfunction of diverse organs throughout the human body. Activated blood elements, release of cytotoxins, complement activation,

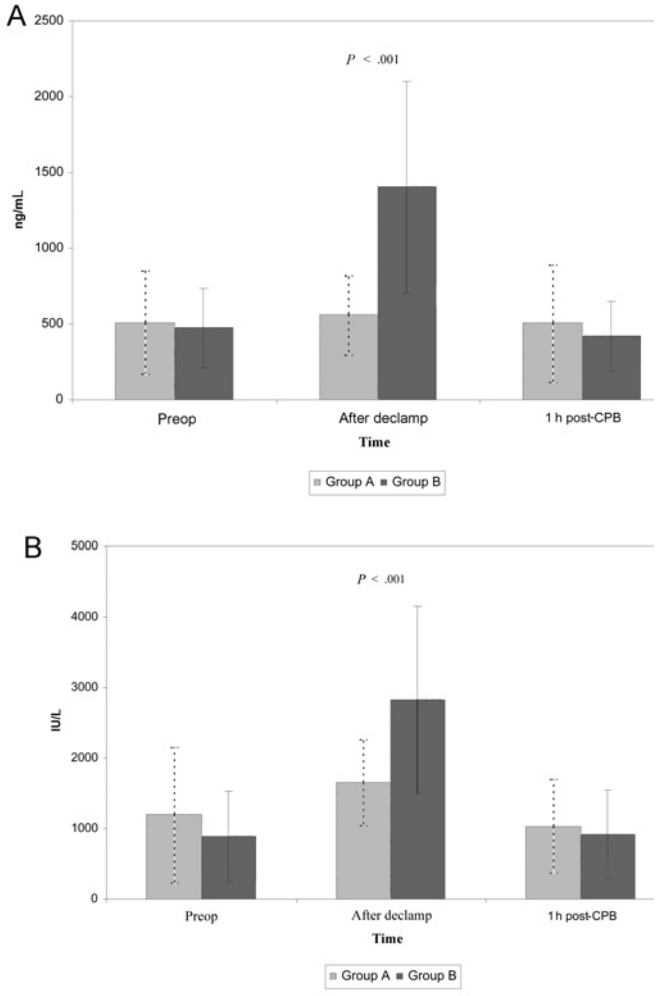

Figure 3. Perioperative values of (A) plasmin-antiplasmin complex and (B) prothrombin fragments 1+2. In both instances, the observed parameters were significantly lower in group A than in group B at the time point following the removal of the aortic clamp.

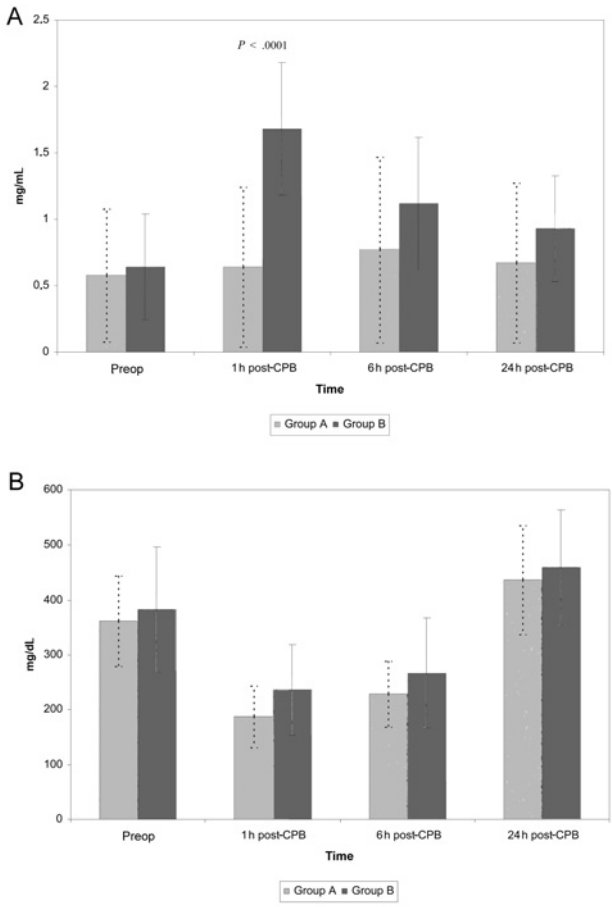

Figure 4. Perioperative values of (A) D-dimers and (B) fibrinogen. In regards to D-dimers, significance in differences was reached at 1 hour after cardiopulmonary bypass.

microparticles obstructing small arterioles, hemodilution, and several other processes dominate this complex pathophysiology [Daniel 1996].

Recent findings in pathophysiology of inflammatory response during open heart surgery report substantial effects of other contributing factors along with CPB, such as operative trauma, regional ischemia-reperfusion injury, endotoxin release, mechanical shear stress, and hypothermia [Jansen 1992; Zahler 1999; Prondzinsky 2005].

A tremendous number of attempts to reduce the damaging effects of CPB have been made in the last decade. New developments of surface coating and modifications were introduced to improve biocompatibility using heparin-coated circuits or other surface-modifying agents in patients undergoing CPB [Gu 1993; Daniel 1996; Muehrcke 1996; Wimmer-Greinecker 1999; Gourlay 2001]; however, these modifications did not universally lead to improved clinical outcomes, simply because even the most thromboresistant biomaterials initiate clotting [Wimmer-Greinecker 1999].

Another novel rationale aiming in the same direction is to reduce the exposure area and priming volume of CPB, theoretically downsizing some of the adverse effects associated with it [von Segesser 2003]. The closed minimized extracorporeal circuit, CorX, reduces standard adult CPB prime volume from more than 1700 mL to only 500 mL, thus limiting the hemodilution seen with conventional CPB. Furthermore, the blood is exposed to only 1.4 m^2 of foreign surface in the CorX, in contrast to 12 m^2 in standard CPB. In addition, the CorX system addresses the issues of venous air handling. The risk of air embolization with associated neurocognitive dysfunction is supposed to be reduced with an AirVac System, which is a sensor regulated venous air handling system.

Table 2. Postoperative Blood Loss and Transfusion Requirements

	Group A	Group B	*P*
Chest drainage in first 12 hours, mL	816 ± 632	707 ± 552	NS
Packed red blood cells in first 24 hours, mL	111 ± 215	126 ± 295	NS
Fresh frozen plasma in first 24 hours, mL	15 ± 97	94 ± 348	NS

Table 3. Assessment of Routine Coagulation Parameters*

		Preoperatively	1h post-CPB	6h post-CPB	24h post-CPB
PTT, sec	Group A	33.1 ± 6.8	48.7 ± 8.9	39.3 ± 4.8	45.4 ± 9.1
	Group B	35.7 ± 5.9	47.7 ± 9.6	41.1 ± 4.6	44.4 ± 9.5
PT, sec	Group A	17.6 ± 4.7	16.9 ± 3.9	15.2 ± 1.5	15.7 ± 2.9
	Group B	18.2 ± 5.1	18.1 ± 5.8	15.7 ± 2.6	14.7 ± 1.4
AT III, %	Group A	102.4 ± 17.4	54.8 ± 9.4	64.3 ± 14.9	77.2 ± 16.9
	Group B	99.4 ± 16.5	56.6 ± 8.7	65.7 ± 17.1	74.3 ± 16.6

*CPB indicates cardiopulmonary bypass; PTT, indicates partial thromboplastin time; PT, prothrombin time; AT III, antithrombin III.

In the present study, the CorX system was compared with standard CPB in arrested heart CABG with regards to the relevant coagulation and clinical parameters. We tested whether the employment of the CorX system would reduce the impact on coagulation and fibrinolytic systems as often experienced with standard CPB. We found that use of a minimized CPB circuit does not permit such a rise in the levels of PAP complex and prothrombin F1+F2 after the removal of the aortic cross clamp, and D-dimers at 1 hour post-CPB as seen following standard extracorporeal circulation. Hemodilution was not so pronounced, either. The other parameters tested regarding both coagulation and clinical outcomes remained similar between groups.

Fallen and co-workers have also compared the CorX system with a standard CPB in patients undergoing CABG in an observational study [Fallen 2003]. They have also detected significantly less hemodilution. In addition, blood product utilization was reduced, contrary to our findings. Overall, patient outcome indices were superior in the CorX group. However, in this and other studies investigating minimized CPB systems [Folliguet 2003; Vaislic 2003], in contrast to our design, most of their patients underwent on-pump beating heart CABG procedures without aortic clamping. In most of these studies the MECC system (Jostra, Hirrlingen, Germany) was mainly used [Fromes 2002; Folliguet 2003; Vaislic 2003; Remadi 2004]. Similar in concept to the CorX system, the MECC system consists of a centrifugal pump and an integrated heat exchanger oxygenator. The priming volume is also very low (about 500 mL) and cardiotomy suction is not used; however, the major difference is that the system is entirely coated with heparin. Furthermore, in regards to de-airing management, there is also an essential difference between both systems. The CorX system is characterized by an automatic de-airing device which is able to stop the pump if too much air is detected. This is an important safeguard for the patient to avoid air embolism. The surgeon is forced to look for the origin of the air leak, which has to be eliminated. In our experience with the CorX system, we had no such a case in which too much air entered the extracorporeal circulation. Anecdotal reports were stated in personal communication, however.

In the present study, we did not see a significant difference between groups in platelet count in the postoperative course. Fromes and associates reported similar results comparing conventional CPB with the MECC system [Fromes 2002], whereas Folliguet and co-workers observed significantly lower platelet counts on postoperative day 1 after using MECC in beating heart CABG procedures [Folliguet 2003]. In an experimental study, in which the CorX system was compared to conventional CPB in calves, the drop of platelets during bypass was significantly pronounced in conventional CPB [Mueller 2002].

The lack of clinical benefit with the CorX system versus conventional CPB in our study is worth speculation. In our opinion, the complex and multivariable pathophysiology behind the proinflammatory and prothrombotic processes triggered by CPB, and more importantly by other potent factors, cannot be blocked by only 1 or 2 means, such as reduced nonendothelial surface area and lower priming volume, but through several more strategies with a common aim working symbiotically. Theoretically, adding other methods to reduce the CPB-damaging effects, such as complement inhibitors, glucocorticoids, or leukocyte filtration, to the use of the CorX system may show a more significant clinical benefit [Edmunds 2004]. It was suggested in a recent study [Prondzinsky 2005] that the surgical trauma may contribute to a higher degree to the proinflammatory status after cardiac surgery than CPB itself. Operating through less invasive approaches may be crucial in bringing the clinical benefit to light.

In conclusion, the CorX system as a minimized closed bypass system leads to reduced coagulation activation; however, a clinical benefit was not detected and may only be achieved by using more complex perfusion strategies.

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