Impact of Heparin- or Nonheparin-Coated Circuits on Platelet Function in Pediatric Cardiac Surgery

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Background. **Extracorporeal circuit coating has been shown to improve coagulation derangements during pediatric cardiopulmonary bypass (CPB). This study compared platelet function and hemostasis activation in pediatric cardiac surgery conducted with nonheparin coating (Balance; Medtronic, Minneapolis, MN) versus heparin-based coating (Carmeda; Medtronic) circuits.**

Methods. **A prospective, randomized, double-center trial was conducted in children older than 1 month undergoing congenital heart disease treatment. Blood samples were collected at baseline (T0), 15 minutes after the start of CPB (T1), and 15 minutes (T2) and 1 hour after the conclusion of CPB (T3). The primary end point of the study was to detect potential differences in β-thromboglobulin levels between the two groups at T2. Other coagulation and platelet function indicators were analyzed as secondary end points.**

Results. **The concentration of β-thromboglobulin increased significantly at T2 in both groups. However, there was no significant difference between the groups across all time points. There was no difference in the secondary end points between the groups.**

Conclusions. **The two circuits showed similar biological effects on platelet function and coagulation. This observation may be useful in optimizing the conduct of CPB and in rationalizing its cost for the treatment of congenital heart disease.**

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Blood is naturally compatible with vascular endothelium but not with artificial surfaces [1]. Hemostatic system activation during cardiopulmonary bypass (CPB) occurs through several mechanisms [2], and platelet activation associated with an increased generation of thrombin results in significant thrombotic risk and increased bleeding in the postoperative period [3]. Infants with congenital heart diseases (CHD) show a highly varied response to anticoagulants [4], and inflammation is certainly an important factor exacerbating hemostatic disorders [5, 6].

To optimize the biocompatibility, extracorporeal circuits have been miniaturized, and the surface coating has been shown to reduce the coagulation derangements [7]. In pediatric CPB, the Carmeda BioActive Surface (Medtronic, Minneapolis, MN) represents a recent attempt to improve biocompatibility. Carmeda is a heparin biosurface with high hydrophilic properties. However, its costs affect the routine use for CHD operations performed with CPB.

More recently, a heparin-free coating, the Balance Bio-Passive Surface (Medtronic) pediatric oxygenation system (Affinity Pixie Oxygenation System; Medtronic), has been developed. It is designed to mimic natural interfaces, as previously described for similar sulfonated polyurethanes [8]. The advertised cost of Balance is significantly lower than that of Carmeda. However, data concerning its use in children is scarce, and these two novel circuits have not yet been compared.

The aim of this study was to compare the biological effect of the Balance-coated CPB system versus the Carmeda heparin-coated system on platelet function and hemostatic activation in children undergoing cardiac operations. The aim was to provide potentially useful insights to optimize the CPB performance and rationalize its costs for the treatment of CHD.

Patients and Methods

Study Design

A prospective, randomized, double-blind, double-center, phase IV noninferiority clinical trial comparing heparin

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Abbreviations and Acronyms

ACT	=	activated clotting time
ADP	=	adenosine 5′-diphosphate
Ao Coarct	=	aortic coarctation
ASD	=	atrial septal defect
β-TG	=	β-thromboglobulin
CAVSD	=	complete atrioventricular septal defect
CD62P	=	P-selectin
CHD	=	congenital heart disease
CI	=	confidence interval
CPB	=	cardiopulmonary bypass
DORV	=	double-outlet right ventricle
F1+2	=	fragment 1+2
HLHS	=	hypoplastic left heart syndrome
IVS	=	intact ventricular septum
L/P	=	leukocyte-platelet conjugates
MA	=	maximum amplitude
PA	=	pulmonary atresia
PAPVD	=	partial anomalous pulmonary venous drainage
PF4	=	platelet Factor 4
PRBC	=	packed red blood cells
TEG-PM	=	thromboelastography platelet mapping
TAT	=	thrombin antithrombin
TOF	=	tetralogy of Fallot
TRAP	=	thrombin receptor activating peptide
T0	=	baseline
T1	=	15 minutes after start of cardiopulmonary bypass
T2	=	15 minutes after the conclusion of cardiopulmonary bypass
T3	=	1 hour after the conclusion of cardiopulmonary bypass
UVH	=	univentricular heart
VSD	=	ventricular septal defect

and nonheparin extracorporeal circuits was conducted (registration number NCT01648712). The local Ethics Committee, Comitato Etico dell'Ospedale Pediatrico Bambino Gesù, approved by study protocol. Parents gave their written informed consent before the enrollment of each child.

Children older than 1 month of age were included and then randomized across two groups, the Carmeda group and the Balance group. Randomization was performed by assigning patient's arms, with lots drawn from sealed envelopes. Exclusion criteria were the presence of chromosomal abnormalities, severe cyanosis, preoperative coagulation disorders, use of circulatory arrest, preoperative use of anticoagulant or antiplatelet drugs, or redo heart operation.

Blood samples were collected at baseline (T0), 15 minutes after the start of CPB (T1), and 15 minutes (T2) and 1 hour after the end of CPB (T3). The primary end point of the study was the detection of potential differences at T2 between the two groups in β-thromboglobulin (β-TG), a platelet α-granule–specific chemokine used as a marker of CPB-related platelet activation [9].

Secondary end points were differences in platelet count, conventional coagulation tests, platelet factor 4 (PF4), another platelet chemokine, and two thrombin generation markers: prothrombin fragment (F1+2) and thrombin-antithrombin complex (TAT). In addition, platelet function was studied by flow cytometry for P-selectin (CD62P) expression and the formation of leukocyte-platelet conjugates [10], and by thromboelastography platelet mapping (TEG-PM) with adenosine 5′-diphosphate (ADP) [11].

Postoperative characteristics over the first 24 postoperative hours were also compared.

Extracorporeal Circulation Setup

According to the protocol for each center, patients in the Carmeda group received a Carmeda-coated Affinity Pixie Oxygenator System with a Carmeda-coated hard shell venous reservoir, a Carmeda-coated affinity pediatric arterial filter, and Carmeda heparin-coated polyvinylchloride tubing. In the Balance group, a Balance-coated Affinity Pixie Oxygenation System and a Balance-coated reservoir were combined with a Balance-coated affinity arterial filter and Balance-coated polyvinylchloride tubing during CPB. The cardioplegia lines were also coated according to the study group.

Anesthesia and Surgical Procedures

After routine anesthesia, all patients received a bolus of heparin (250 IU/kg) to achieve an activated clotting time longer than 400 seconds during CPB. CPB was performed under moderate hypothermia. Myocardial protection was achieved by anterograde blood cardioplegia, according to each center's protocol. Post-CPB heparin neutralization was achieved with 2.5 mg/kg protamine sulfate up to confirmation of activated clotting time (Hemochron Jr; International Technidyne Corporation, Edison, NJ) return to baseline level. In case of persistent bleeding after activated clotting time normalization, the attending anesthesiologist determined the requirement for platelets transfusion (Table 1).

Data Collection and Blood Assays

Demographic data, type of CHD and surgical treatment, and intraoperative and postoperative characteristics in the first 24 hours were recorded. Blood samples withdrawn from the arterial line at T0, T1, T2, and T3 were collected in Vacutainer tubes (BD Vacutainer System, Plymouth, UK). For hemostasis testing, blood was collected in 0.109 mol/L sodium citrate or in citrate theophylline adenosine and dipyridamole blood collection tubes (ratio: 1:9 vol/vol). For TEG-PM, blood was also collected in lithium heparin. Blood specimens were immediately delivered by hand to the laboratory [12, 13].

Blood was analyzed within 30 minutes. Platelet-poor plasma was prepared from citrated and citrate theophylline adenosine and dipyridamole blood by centrifugation at 2,500*g* for 20 minutes at 20°C and 4°C, respectively.

Table 1. Patient Characteristics According to the Group

Variables[a]	Balance[b] (n = 24)	Carmeda[b] (n = 22)	*p* Value
Demographics			
Age, days	853.8 ± 753.9	625.5 ± 707.1	0.68
Weight, kg	11.7 ± 2.7	12.1 ± 2.68	0.44
Procedure			
CPB duration, minutes	105.7 ± 51.9	114.6 ± 44.3	0.3
Aortic cross-clamping duration, minutes	65.9 ± 46.4	56.4 ± 42.3	0.72
CPB temperature, °C	33.0 ± 3.3	32.2 ± 4.5	0.83
Conventional ultrafiltration, mL	710 ± 552.2	584.1 ± 298.2	0.64
Platelet transfusion	11 (46)	7 (32)	0.55
Tranexamic acid intraoperatively	13 (54)	11 (50)	0.92
PRBCs intraoperatively, IU	16 ± 67	13 ± 59	0.37
Preoperative characteristics			
Hemoglobin, g/dL	12.63 ± 2.08	14.13 ± 2.75	0.01[c]
Platelet count, $\times 10^9$/L	321.79 ± 73.66	296.9 ± 96.31	0.08
Fibrinogen concentration, g/L	2.73 ± 1.15	2.89 ± 0.69	0.63
Prothrombin time, %	87.26 ± 9.44	94.14 ± 8.98	0.04[c]
Postoperative characteristics			
Hemoglobin, g/dL	13.58 ± 1.43	14.43 ± 1.71	0.17
Platelet count, $\times 10^9$/L	161.25 ± 59.58	140.82 ± 57.58	0.36
Fibrinogen concentration, g/L	2.1 ± 1.03	1.81 ± 0.45	0.33
Prothrombin time, %	81.25 ± 16.49	76.32 ± 15.07	0.47
Bleeding, mL/kg per 24 hours	0.59 ± 0.47	1.26 ± 2.6	0.22
Platelet transfusion, No.	1	0	0.41
Transfusion, mL/kg per 24 hours			
Fresh frozen plasma	4.17 ± 20.41	10.32 ± 48.4	0.95
Cell-saving device	9.17 ± 35.74	10 ± 26	0.66
PRBC	30.83 ± 51.07	5.23 ± 17.49	0.11
Duration of mechanical ventilation, hours	8.35 ± 7.28	8.64 ± 6.44	0.55
Intensive care unit length of stay, days	2.17 ± 1.34	2.64 ± 2.75	0.78

[a] Continuous data are expressed as mean ± SD and categorical data as number (%). [b] Medtronic, Minneapolis, MN. [c] Statistically significant ($p < 0.05$).

CPB = cardiopulmonary bypass; PRBC = packed red blood cells.

These samples were used immediately for automated testing or frozen in aliquots and stored at –80°C until analysis. Conventional laboratory variables were assessed at each study time. Platelet count, hematocrit, and hemoglobin values were measured using Sysmex XE 5000 (Siemens Healthcare Diagnostics, Marburg, Germany). Fibrinogen levels, activated partial thromboplastin time, prothrombin time, and antithrombin levels were measured using ACLTop (Werfen Instrumentation Laboratory, Bedford, MA).

Platelet-poor plasma β-TG, PF4, TAT, and F1+2 were measured at each study time by an enzyme-linked immunosorbent assay. β-TG and PF4 (Diagnostica Stago, Asnières sur Seine, France) were assessed in plasma obtained from citrate theophylline adenosine and dipyridamole tubes and F1+2 and TAT (Siemens Health Diagnostics) in plasma from citrate tubes. Platelet function was assessed by flow cytometry in citrate whole blood, as previously described, using FACS Canto II and DIVA software from Becton Dickinson (BD Biosciences, San Jose, CA) [14]. The percentage leukocyte-platelet conjugates and the number of positive events for CD62P before and after thrombin receptor activating peptide activation were measured at T0 and T2. TEG-PM (Haemonetics, Braintree, MA) response to ADP was measured at T0, T1, and T2.

Statistical Analysis

Sample size calculation was based on previous studies [9, 15], and the number of patients per arm, to ensure a power of 80%, was set at 24 by establishing a noninferiority difference between the group at 180 ng/mL and a SD of 250 ng/mL. Because of the difference observed in β-TG between the groups at T0 as a result of the high interindividual variability in the β-TG assay [16, 17], only the proportion of variation relative to T0 was analyzed. Its significance threshold was set at +120%, based on the report by Kirshbom and colleagues [9].

To test for noninferiority, the difference between the groups in β-TG proportions of variation relative to baseline was calculated at each time point. The 95% confidence intervals (CIs) were estimated by boot strapping with 1,000 resamples. The difference was considered

Table 2. Diagnoses of Enrolled Patients in Each Group

Diagnosis	Carmeda[a] (n = 24) No.	Diagnosis	Balance[a] (n = 22) No.
Ao Coarct and VSD	1	Absent pulmonary valve	1
ASD with PAPVD	2	Aortic stenosis	1
CAVSD	3	ASD with PAPVD	1
DORV with VSD	1	CAVSD	4
HLHS/UVH	3	HLHS/UVH	1
PA with VSD	1	PA with IVS	2
Pulmonary stenosis	1	PA with VSD	2
Subaortic membrane	1	Pulmonary stenosis	1
Tricuspid atresia	1	Tricuspid atresia	1
TOF	3	TOF	3
VSD	5	VSD	7

[a] Medtronic, Minneapolis, MN.

Ao Coarct = aortic coarctation; ASD = atrial septal defect; CAVSD = complete atrioventricular septal defect; DORV = double outlet right ventricle; HLHS/UVH = hypoplastic left heart syndrome/univentricular heart; IVS = intact ventricular septum; PA = pulmonary atresia; PAPVD = partial anomalous pulmonary venous drainage; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

clinically acceptable if the upper limit of the 95% CI exceeded 120%.

Nonparametric tests were used to compare baseline variables and secondary end points between groups. Continuous variables were compared using the Kruskal-Wallis stratified rank sum test, and categorical variables were compared using a Cochran-Mantel-Haenszel statistic for small samples [18]. Analysis of variance was used to compare results at different time points, with post hoc analysis for multiple comparisons when necessary. Missing data were ignored. Analyses were performed using R software (www.r-project.org).

Results

Demographic and Perioperative Data

The study included 48 patients between March 2013 and April 2015, with 24 in the Balance group and 22 in the Carmeda group. Two patients in the Carmeda group were withdrawn after enrollment because of the unplanned rescheduling of the operation after the sealed envelope was broken. Demographic and perioperative data are summarized in Tables 1 and 2. There were no significant differences in baseline and perioperative data between the two groups, except for preoperative prothrombin time and hemoglobin, which had no clinical relevance (Table 1).

Analysis of β-TG

At T0, the mean β-TG level was 214.91 ± 168.07 ng/mL in the Balance group and 150.05 ± 140.84 ng/mL in the Carmeda group, with a mean difference between the groups of 80 ng/mL (95% CI, –14.87 to 174.68 ng/mL). As

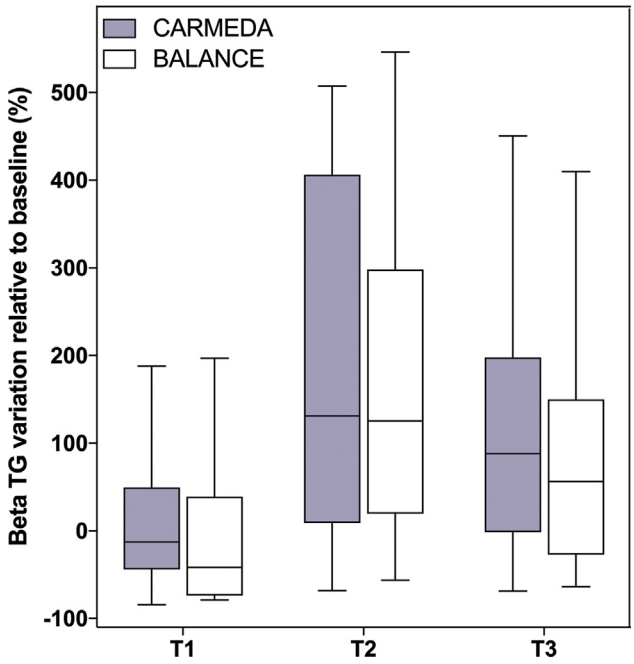

Fig 1. Variation in β-thromboglobulin (TG) relative to baseline at 15 minutes after the start of cardiopulmonary bypass (T1) and at 15 minutes (T2) and 1 hour after the conclusion of cardiopulmonary bypass (T3). The horizontal lines represent the 5th percentile, 25th percentile, median, 75th percentile, and 95th percentile from the bottom to the top. Gray boxes: Carmeda group (Medtronic, Minneapolis, MN); white boxes: Balance (Medtronic) group.

time progressed, the mean β-TG levels increased significantly in both the Balance and the Carmeda groups during CPB: 108.38 ± 45ng/mL and 107.67 ± 49.84 ng/mL at T1, 387.43 ± 234.3 ng/mL and 280.1 ± 164.63 ng/mL at T2, and 341.04 ± 311 ng/mL and 248.19 ± 159.85 ng/mL at T3, respectively ($p = 0.003$ for Balance, $p = 0.009$ for Carmeda). The difference in β-TG proportions of variation relative to baseline between the Balance and the Carmeda groups was –19.55% (95% CI, –56.35% to 16.80%) at T1, –19.02% (95% CI, –80.19% to 89.02%) at T2, and –50.82% (95% CI, –239.07% to 78.36%) at T3. This was not considered significant (Fig 1).

Analysis of Other Coagulation and Platelet Parameters

The common hematologic indicators changed as expected during CPB, with a significant decrease in platelet count and fibrinogen concentration compared with baseline values, particularly at T1 and T2 (all $p = 0.0001$; Table 3), without differences at any time point between the groups.

PF4 levels were not different between the groups, remaining stable during and after CPB (Table 3).

Platelet activation, studied by flow cytometry and TEG-PM, also showed no significant differences between the two groups (Table 3). The platelet-positive percentage for CD62P was similar after CPB (T2) compared with preoperative values. However, the leukocyte-platelet conjugates decreased after the conclusion of CPB ($p = 0.0001$ for both groups). The CD62P increase induced by

Table 3. Difference in Biological Data Between Balance and Carmeda Patients[a]

Variable	Time	Absolute Concentration (mean ± SD)		Mean Difference (95% CI)	
		Balance[b] (n = 24)	Carmeda[b] (n = 22)	Balance-Carmeda	*p* Value[c]
Platelet count, $\times 10^9$/L	T0	177.2 ± 67.29	157.7 ± 93.86	19.56 (–22.38 to 61.5)	0.42
	T1	118.38 ± 51.33	104.27 ± 52.23	14.1 (–27.84 to 56.04)	0.36
	T2	89.29 ± 38.47	80.45 ± 42.53	8.83 (–33.1 to 50.78)	0.46
	T3	108.79 ± 41.04	96.77 ± 45.38	12.02 (–29.92 to 53.96)	0.35
Fibrinogen, g/dL	T0	237 ± 73	231 ± 72.6	6.06 (–37.29 to 49.42)	0.78
	T1	155.8 ± 53	150 ± 50.7	5.75 (–25.09 to 36.59)	0.71
	T2	171 ± 57	163 ± 42.4	8.41 (–21.46 to 38.29)	0.57
	T3	191 ± 56	176 ± 39.6	14.98 (–13.56 to 43.51)	0.29
Antithrombin, %	T0	92.6 ± 14.8	86.8 ± 12.9	5.80 (–12.29 to 23.9)	0.17
	T1	80.75 ± 31.08	74.29 ± 25.02	6.46 (–11.39 to 24.31)	0.44
	T2	83.56 ± 25.09	81.56 ± 27.57	2.00 (–16.09 to 20.09)	0.8
	T3	85.83 ± 21.97	82.9 ± 25.17	2.93 (–15.1 to 20.97)	0.68
PF4, IU/mL	T0	86.4 ± 75.42	74.43 ± 85.14	11.96 (–37.22 to 61.15)	0.62
	T1	90.54 ± 43.82	92.19 ± 48.11	–1.65 (–29.5 to 26.2)	0.9
	T2	70.52 ± 54.27	51.71 ± 68.52	18.8 (–19.1 to 56.7)	0.32
	T3	90.0 ± 106.84	68.1 ± 61.82	21.9 (–30 to 73.8)	0.39
TAT, μg/L	T0	23.4 ± 65.2	12.9 ± 13.5	10.5 (–18.2 to 39.3)	0.45
	T1	7.9 ± 12.14	8.32 ± 4.54	–0.48 (–5.8 to –5.0)	0.87
	T2	57.98 ± 53.16	43.17 ± 32.2	14.8 (–11.36 to 40.96)	0.26
	T3	50.18 ± 31.17	51.7 ± 34.98	–1.5 (–21.7 to 18.7)	0.88
F1+2, pmol/L	T0	229.13 ± 98.07	249 ± 154.53	–19.87 (–1,519 to 1,479)	0.61
	T1	316.29 ± 308.77	281.71 ± 125.89	34.58 (–1,449 to 1,518)	0.6
	T2	3,517.2 ± 4,481.31	1,724.0 ± 1,608.22	1,793 (–214.6 to 3,801)	0.07
	T3	2,489 ± 2,215	1,832 ± 1,277	657.3 (–857.7 to 2,172)	0.23
ACT, seconds	T0	124.04 ± 17.13	128.95 ± 19.58	–4.913 (–57.43 to 47.6)	0.37
	T1	449.42 ± 122.58	455.41 ± 128.05	–5.992 (–58.51 to 46.52)	0.87
	T2	135.96 ± 17.19	133.91 ± 11.9	2.049 (–50.47 to 54.57)	0.63
L/P conjugates (% of positive events for both CD45 and CD41)	T0	17.12 ± 5.5	17.82 ± 5.9	–0.66 (–4.20 to 2.86)	0.7
	T2	10.41 ± 3.74	10.46 ± 3.35	–0.04 (–2.15 to 2.05)	0.96
CD62P, % positive events	T0	6.2 ± 8.33	7.29 ± 7.44	–1.09 (–5.89 to 3.71)	0.64
	T2	7.52 ± 15.13	5.6 ± 8.25	1.91 (–5.46 to 9.29)	0.6
CD62P TRAP, % positive events	T0	54.1 ± 27.8	64.24 ± 25.75	.14 (–26.45 to 6.16)	0.21
	T2	42.02 ± 32.38	47.94 ± 29.03	–5.92 (–24.61 to 12.76)	0.52
TEG-PM ADP, % of platelet inhibition	T0	28.13 ± 24.39	27.33 ± 32.04	0.8 (–18.03 to 19.63)	0.93
	T1	46.12 ± 28.46	35.84 ± 34.2	10.28 (–9.8 to 30.41)	0.3
	T2	75.86 ± 25.45	74.79 ± 28.01	1.07 (–6.28 to 18.43)	0.9
TEG-PM with kaolin MA, mm	T0	62.34 ± 5.79	61.03 ± 5.53	1.31 (–2.26 to 4.89)	0.46
	T1	50.25 ± 9.79	46.48 ± 6.57	3.77 (–1.31 to 8.86)	0.14
	T2	51.76 ± 7.30	48.68 ± 5.65	3.08 (–0.96 to 7.12)	0.13

[a] Data are depicted as absolute concentrations and as mean difference with the 95% CI confidence interval [b] Medtronic, Minneapolis, MN. [c] The *p* value concerns the difference between Balance and Carmeda groups.

ACT = activated clotting time; ADP = adenosine 5′-diphosphate; CD62P = P-selectin; CI = confidence interval; F1+2 = fragment 1+2; L/P = leucocyte-platelet conjugates; MA = maximum amplitude; PF4 = platelet factor 4; TAT = thrombin/antithrombin complex; TEG-PM = thromboelastography platelet mapping; TRAP = thrombin receptor activating peptide; T0 = baseline; T1 = 15 minutes after start of cardiopulmonary bypass; T2 = 15 minutes after the conclusion of cardiopulmonary bypass; T3 = 1 hour after the conclusion of cardiopulmonary bypass.

60 μmol/L of thrombin receptor activating peptide was weaker at T2 than at T0 ($p = 0.002$ in the Balance group and $p = 0.0001$ in the Carmeda group), as previously described [14]. In the same way, the inhibition of platelet response to ADP increased during CPB ($p = 0.0003$ in the Balance group and $p = 0.001$ in the Carmeda group).

The levels of the TAT and F1+2 were not statistically different between the groups, although a higher F1+2 level was observed in the Balance group after CPB at T2 (2,517.2 ± 4,481.31 vs 1,724 ± 1,608.22 pmol/L; $p = 0.07$) and at T3 (2,489 ± 2,215 vs 1,832 ± 1,277 pmol/L; $p = 0.23$). After the conclusion of CPB, there was a significant

increase in both groups for TAT ($p = 0.0001$ and $p = 0.001$ in Balance and Carmeda, respectively) and F1+2 ($p = 0.001$ and $p = 0.0001$ in Balance and Carmeda, respectively).

Clinical Outcomes

We found no differences in postoperative characteristics over the first 24 postoperative hours (Table 1). Patients who did not receive intraoperative platelet transfusions had significantly lower β-TG values than those who received platelet transfusions at T2 (265.7 ± 150.8 vs. 448.1 ± 242.2 ng/mL; $p = 0.01$) and at T3 (176 ± 123 vs. 479.1 ± 292.2 ng/mL; $p < 0.0001$).

Comment

A surface-modified bypass circuit should limit hemostatic complications occurring in pediatric cardiac CPB. This study shows that coating the circuits with heparin or hydrophilic polymer does not change the effect of CPB on platelet function and coagulation in children. Platelet activation was evaluated by the quantification of platelet granule–specific chemokines [9, 19]. In particular, the modification of β-TG levels was chosen as the primary end point, because the concentration of β-TG in plasma had already been described as a good marker of in vivo platelet activation and had been used to study age-related differences in platelet reactivity to CPB [19]. Moreover, Kirshbom and colleagues [9] previously demonstrated that mean β-TG levels peaked at the conclusion of bypass in children operated on for CHD.

Our results confirmed a peak of β-TG at the conclusion of CPB and failed to show any statistical difference between the two groups. This suggests that Balance surface circuits have the same effect on platelet function during CPB as Carmeda circuits. In the same way, the concentrations of PF4 showed no differences between the two groups. In contrast to β-TG, however, their concentrations were stable both during and after CPB (Table 3). The high concentration of heparin used in CPB probably complicated the interpretation of the PF4 levels in this context [20].

To assess the platelet dysfunction, markers of platelet activation were studied using different methods (flow cytometry and TEG-PM). Again, we found no significant difference between the two groups. The percentage of positive events indicating CD62P expression in the basal condition did not increase after CPB and neither did the platelet-leukocyte conjugates. After thrombin receptor activating peptide–induced platelet activation, CD62P was weaker at T2 than at T0, as previously described [14]. TEG-PM analysis revealed that the sensitivity of platelets to ADP decreased during CPB to an equal extent in both groups. Altogether, these results confirmed the deleterious effect of CPB on platelet function, regardless of the coating of the circuit.

As expected, the levels of the TAT and F1+2 were significantly increased at the conclusion of CPB [21], without significant differences between the two groups, indicating an equivalence of the two circuits regarding the activation of the coagulation system. From a clinical standpoint, there were no statistical differences between the two circuits. Interestingly, patients who received platelet transfusions after their operation were those with the highest β-TG levels, regardless of the circuit used [19].

With respect to the literature, data on the use of Carmeda circuits in children compared with identical noncoated circuits suggest a decrease in inflammatory response similar to that observed in the adult population [7]. Lower concentrations of β-TG were also observed for the heparin-coated CPB circuits [22]. However, Carmeda circuits have not gained acceptance for routine open heart operations, mainly because of their elevated costs. Consequently, various heparin-free biosurface-coated circuits have been developed and compared with uncoated and heparin-coated circuits, respectively [21, 23, 24].

Our findings confirm that the biological effects of heparin-coated (Carmeda) and nonheparin-coated (Balance) circuits for CHD operations are similar in platelet and coagulation activation.

Study Limitations

This study has some strengths and weaknesses. Although the overall sample size was not large, the number of patients was sufficient to conduct a noninferiority study. β-TG showed a wide interindividual variability, which may impede its reliability as an optimal biomarker. The loss of two study circuits resulted in a slightly lower Carmeda population with respect to the anticipated sample size. However, the overall β-TG modification over time confirmed the noninferiority of the Balance circuit. These results would not have been significantly altered by the presence of additional patients.

Conclusion

Carmeda and Balance circuits have similar effects on platelet function in pediatric cardiac surgery. This observation appears extremely useful in optimizing the conduct of CPB and in rationalizing its cost, particularly for high-volume centers treating children with CHD.

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