

An *ex vivo* evaluation of blood coagulation and thromboresistance of two extracorporeal circuit coatings with reduced and full heparin dose[†]

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Abstract

OBJECTIVES: Bioactive Carmeda® heparin-coated extracorporeal circuits (ECCs) have been shown to reduce contact phase and coagulation activation during cardiopulmonary bypass (CPB). Heparin coating is therefore effective in safely reducing coagulation during routine CPB. Balance® Biosurface is a new, recently developed biopassive coating containing negatively charged sulphonated polymers. This study sought to compare the clotting activation and thromboresistance of the Balance® (B) circuit with that of the Carmeda® (C) with full-dose systemic heparin (FDH) and reduced-dose systemic heparin (RDH).

METHODS: This *ex vivo* study set-up comprising 40 experiments consisted of simplified ECC and circulation of freshly donated human blood. RDH and FDH regimens were obtained with 0.5 IU/ml and 1 IU/ml heparin administered to reach target activated clotting times (ACTs) of 250 and 500 s, respectively. The study design comprised four groups: FDH-C, FDH-B, RDH-C and RDH-B (all $n = 10$). Blood was sampled prior to and during the 2-h CPB. Coagulation activation was assessed (FXIIa, F1.2) and electron microscope scan imaging of oxygenators enabled determination of adhesion scores.

RESULTS: With a biopassive compared with bioactive surface, mean ACT was lower, regardless of the heparin regimen applied ($P < 0.001$), whereas the total heparin dose required to maintain ACT was above target level ($P < 0.001$). However, FXIIa and F1.2 values were similar in all groups throughout, as were pressure gradients among oxygenators. All groups demonstrated similar adhesion scores following ultra-structural oxygenator assessment.

CONCLUSIONS: In the absence of surgical-related haemostatic disturbances and based on target ACT levels under reduced- or full-dose heparin, the clotting process was similar to heparin-coated and new sulphonated polymer-coated ECC, both demonstrating similar thromboresistance.

Keywords: Cardiopulmonary bypass • Surface coating • Thromboresistance • Coagulation

INTRODUCTION

Cardiopulmonary bypass (CPB) causes coagulation activation when blood comes into contact with artificial surfaces. To avoid circuitry blood clotting and thromboembolic complications, systemic heparin is administered to both the patient and circuits, in line with protocols laid down in the 70 s [1, 2]. Standard practice dictates that 300 IU/kg heparin be associated with 5000 IU in the prime volume, despite this practice being based on weak evidence regarding appropriate patient anticoagulation. Some authors have,

in fact, reported that this full-dose anticoagulation approach unnecessarily exposes the patient to excessive blood loss [3]. On the other hand, safe, low systemic anticoagulation protocols have been developed utilizing a comprehensive strategy comprising biocompatible closed circuits, retrograde autologous prime, routine use of cell saver, antifibrinolytics and dedicated point-of-care devices for determining adequate heparin and protamine doses [4–6]. Of all biocompatible circuits, Bioactive Carmeda® heparin coating is currently the most available having undergone extensive assessment in a low systemic anticoagulation setting [7, 8]. This strategy produced a very satisfactory clinical outcome with no signs of clotting [8], also offering the possibility of alleviating clopidogrel-related complications in patients undergoing coronary artery bypass grafting [9].

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Balance® Biosurface is a newly available biopassive coating containing negatively charged sulphonated polymers, which has been proposed as an alternative to the highly heparin-loaded Bioactive Carmeda® heparin coating. Yet, the thromboresistance of such a new surface modification remains unknown, particularly concerning reduced anticoagulation during CPB. This study sought to compare the clotting activation and thromboresistance of the Balance® (B) circuit with that of the Carmeda® (C) by way of a simulated CPB loop with full-dose systemic heparin (FDH) and reduced-dose systemic heparin (RDH).

MATERIALS AND METHODS

Study design and blood collection

This study was performed *ex vivo* using a simplified extracorporeal circuit (ECC) containing human blood [10] provided by the French Establishment of Blood (EFS). Healthy adult donors were randomly selected by the EFS, having provided written informed consent and having been fully informed of the non-therapeutic use of the donated blood. Adults undergoing antiaggregant platelet therapy were excluded from donation. Blood was collected into a 600 ml maximal volume pack (Fenwal®, Inc., Lake Zurich, IL, USA), containing 66.5 ml anticoagulant citrate phosphate dextrose, on each study-day morning.

Forty experiments were conducted, categorized into four experimental groups outlined in a 2 × 2 plan. This enabled comparison to be made between the two coating system types, namely Bioactive Carmeda® and Balance® Biosurface (Medtronic, Minneapolis, MN, USA), and two anticoagulation regimens, of full-dose and reduced-dose heparin, in the following manner:

- (i) Group 1: full-dose heparin and Carmeda® (FDH-C)
- (ii) Group 2: full-dose heparin and Balance® (FDH-B)
- (iii) Group 3: reduced-dose heparin and Carmeda® (RDH-C)
- (iv) Group 4: reduced-dose heparin and Balance® (RDH-B)

The Angers University Hospital's Clinical Research Center randomly allocated the experiment order sequence, and its medical ethics committee approved the study set-up.

The blood bag was divided into two equal parts, with one stored for 3 h at ambient temperature in a constantly moving state (Hemomatic, Hemopharm SA, Gardanne, France) in order to preserve platelet properties [11]. One blood sample was taken to record baseline activated clotting time (ACT) and another with a 3.0 ml tube containing ethylenediamine tetra-acetic acid was taken to determine baseline blood cell count.

On each study day, two experiments were conducted to enable a meaningful comparison of the two circuit coatings using the same donated blood and heparin dosage.

To achieve target ACT, 0.5 IU/ml or 1 IU/ml heparin was added to the blood pack according to the RDH (target ACT at 250 s) or FDH (target ACT at 500 s) anticoagulation regimen, respectively.

Two blood samples were then taken to determine the ACT and blood cell count analysis prior to CPB initiation.

Ex vivo simulated cardiopulmonary bypass

The heart-lung machine used to simulate extracorporeal circulation was specifically designed and simplified for this study. It was composed of low-volume paediatric materials, including a 48 ml

membrane oxygenator (Affinity Pixie® Hollow Fiber Oxygenator, Medtronic, Minneapolis, MN, USA), a soft-shell reservoir with an 800 ml maximum volume and circuitry tubing of around 83 ml in volume (1/4 × 1/16 ×, all Medtronic S.A.S., Boulogne-Billancourt, France). A mechanical roller pump circulated the blood (COBE Perfusion System, Lakewood, CA, USA).

The priming volume consisted of 175 ml sodium bicarbonate 1.4% and 325 ml sodium chloride 0.9%, and was circulated for several minutes at 37°C maintained by a heat exchanger (Medtronic Bio Cal®; Medtronic Bio. Medicus, Inc., Eden Prairie, MN, USA). Once the process was completed, the pump was stopped, and a maximum possible priming volume was removed from the soft-shell reservoir. The prepared blood was then added and a retrograde autologous prime process conducted in order to remove excess priming from within the circuitry and attain a haematocrit of between 20 and 30%. Following this, 2-h CPB commenced. During the procedure, standard clinical conditions were simulated in terms of haemodilution, normothermia, perfusion flow (2.4 l/min/m²) and gas exchange (pH 7.35–7.45, pCO₂ < 50 mmHg and pO₂ < 150 mmHg), controlled by a blood parameter monitor (CDI 500; Terumo, Cardiovascular System Corp., Tustin, CA, USA).

Throughout, ACT was controlled by the Hepcon® Heparin Management System HMS Plus (Medtronic Hemotec, Inc., Englewood, CO, USA), which maintained ACT at the target level with respect to RDH or FDH anticoagulation regimen.

For accurate simulation of arterial blood conditions, sodium bicarbonate was used for the dilution volume, and air was added during the first three minutes of the experiment at 200 ml/min by means of an air and oxygen distributor (Maquet Cardiopulmonary AG, Hirrlingen, Germany) connected to an air bottle (Medical Rebuild Air, Air Liquide, Paris, France) and oxygen bottle (Medical Oxygen, Air Liquide, Paris, France). Preoxygenator pressure was calculated based on the preoxygenator line (HG0283 ¼ × ¼ LL Maquet Cardiopulmonary Bypass, Hirrlingen, Germany), and postoxygenerator pressure was measured with a preprepared connector.

Blood sampling and biological measurements

Blood samples (18 ml per time point) were taken on blood perfusion initiation (T0), then at 10 (T10), 60 (T60) and 120 (T120) min. These were used to measure haematocrit, haemoglobin, red blood cell count, platelet count, leucocyte count, ACT, pO₂, pCO₂ and pH, following standard laboratory procedure.

Activation of coagulation and leucocytes. Aliquots of citrated or ethylenediamine tetra-acetic acid plasma were prepared for each experiment and stored at –80°C until analysis by the haematology laboratory. Biological parameters for thromboresistance and blood activation were analysed using enzyme-linked immunosorbent assay (ELISA) kits for prothrombin fragment 1 + 2 (F1.2) and Factor XIIa (Euromedex, Uscn Life Science, Inc., Souffelweyheim, France). Leucocyte activation was assessed through neutrophil elastase release and analysed using ELISA kits (AssayMax Human Neutrophil Elastase, AssayPro, St Charles, MO, USA)

Electron microscopy and scoring

The filters were sent to the Common Service of Imagery and Medical Analysis for analysis of cellular and fibrin deposits on the grid by means of an electron-scanning microscope. This procedure

consisted of cutting four 1 cm² fragments, post-fixation with osmium tetroxide 1% (OsO₄), dehydration with ethanol, desiccation with hexamethyldisilazane and metallization with a carbon-coating layer. Adhesion scoring was assessed by applying Borowiec's method for arterial filters, established in his 1993 study [12]. This method is based on the morphological cell variations and the degree of artificial surface covering by cells and fibrin, categorized into 10 grades as follows: Grade 1: absence of surface adhesion and morphological modifications; Grade 3: moderate presence of cellular activation signs, such as adhesion commencement and occasional fibrin fibres; Grade 6: increased activation, with cells exhibiting multiple pseudopodia and aggregates forming in platelets and leucocytes and Grade 10: cellular adhesions and broad deposits containing non-identifiable cells. Grades not included above were intermediate forms. Four fields of each sample were analysed by microscope with ×750 magnification. The final grade of adhesion was to be calculated from an arithmetic mean of each adhesion grade per field.

Statistics

There was no power calculation performed for the study due to weak evidence in the literature regarding scanning electron microscope ranking and as we aimed to limit the number of

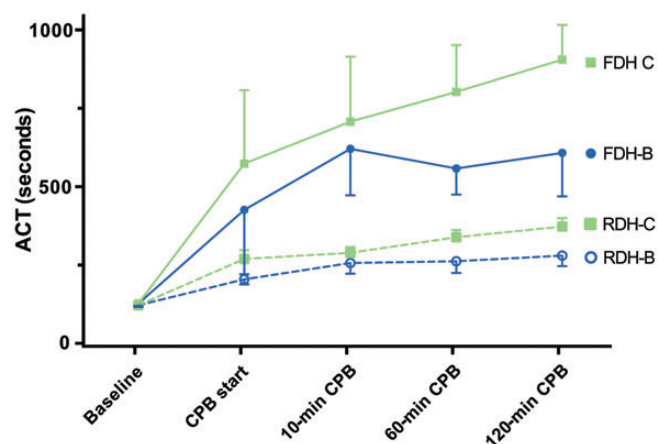


Figure 1: Activated clotting time (ACT) during perfusion showing pre- and intraexperimental states. Data are presented as mean ± SD. FDH-C: full-dose heparin + Carmeda® coating; FDH-B: full-dose heparin + Balance® coating; RDH-C: reduced-dose heparin + Carmeda® coating; RDH-B: reduced-dose heparin + Balance® coating. Repeated-measures ANOVA revealed a significant difference among the groups ($P < 0.001$). *Post hoc* analysis showed no difference between the Balance® or Carmeda® RDH protocol ($P = 0.55$), while other group comparisons all revealed a difference (all $P < 0.001$).

required blood donors to a minimum. In order to reduce variation in our results, one blood donation was used for two separate experiments in a randomized fashion.

Data were recorded and analysed using the SPSS software package (IBM SPSS Statistics 20, New York, NY, USA). Continuous data were presented as mean ± standard deviation (SD) when normally distributed, according to the Kolmogorov–Smirnov test, and analysed by analysis of variance (ANOVA). Changes in biological end points with time to baseline relative values were assessed by three-way repeated-measures ANOVA for four groups with type of circuit and level of anticoagulation as fixed factors. Bonferroni analysis was used for *post hoc* analysis.

Non-parametric tests were conducted for adhesion score comparison as a semiquantitative data value (ordinal ranking) expressed as a median (25th–75th percentiles). All groups were subject to the Kruskal–Wallis test. For all tests, P -values < 0.05 were considered statistically significant.

RESULTS

Anticoagulation during simulated cardiopulmonary bypass

Blood donations originated from 11 men and 9 women aged 46 ± 11 years. Given that donated blood in each pack had been exposed to both coating systems, all blood exhibited similar pre-experimental biological characteristics between exposure to Bioactive Carmeda® and Balance Biosurface® coatings, and experimental sequence order was not seen to have any impact, with haematocrit (%) of 37.8 ± 2.9 vs 37.7 ± 3.2 , leucocytes ($\times 10^9/l$) of 4.5 ± 1.3 vs 4.6 ± 1.3 , platelets ($\times 10^9/l$) of 201 ± 47 vs 202 ± 51 and ACT (in seconds) of 127 ± 6 vs 127 ± 7 , respectively.

Sequential ACT pattern is shown in Fig. 1, illustrating that the FDH protocol resulted in higher ACT levels during CPB than the RDH protocols. Repeated-measures ANOVA revealed a significant difference among the groups ($P < 0.001$). *Post hoc* analysis showed no difference between the Balance® or Carmeda® RDH protocol ($P = 0.55$), while other group comparisons all revealed a difference (all $P < 0.001$).

Mean ACT at each determination point was under 400 s with RDH and over 400 s with FDH. Total heparin dose administered throughout the study differed between the groups ($P < 0.001$) (Table 1). Regardless of the heparin regimen administered, mean ACT was lower with the biopassive Balance Biosurface® compared with Bioactive Carmeda® coating, whereas total heparin dose used to maintain ACT above target level was higher with the former.

Table 1: Anticoagulation

	Group 1 FDH-C (n = 10)	Group 2 FDH-B (n = 10)	Group 3 RDH-C (n = 10)	Group 4 RDH-B (n = 10)
Total dose of heparin (IU)	475 ± 125	577 ± 110	220 ± 35	309 ± 26
Lowest ACT (s)	355	221	227	184
Highest ACT (s)	1000	1000	404	362
Mean ACT (s) after heparin administration	703	539	313	260

Data are given as mean ± SD or absolute numbers.

FDH-C: full-dose heparin + Carmeda® coating; FDH-B: full-dose heparin + Balance® coating; RDH-C: reduced-dose heparin + Carmeda® coating; RDH-B: reduced-dose heparin + Balance® coating; ACT: activated clotting time.

Blood gases and blood cell counts

Physiological ranges were maintained throughout the experiments for pH (range 7.36–7.51), pO_2 (range 129–164 mmHg) and pCO_2 (range 33–61 mmHg), as illustrated in Fig. 2. Repeated-measures ANOVA revealed an overall difference among the groups for pH ($P < 0.004$), which was based on a distinction in the course of pH over time between the Balance® RDH and the Carmeda® FDH groups ($P = 0.002$). The pO_2 ($P = 0.29$) and pCO_2 ($P = 0.07$) were not different among the groups.

Simulation of haemodilution at a clinically relevant level was successful, as demonstrated by initial haematocrit, leucocyte and

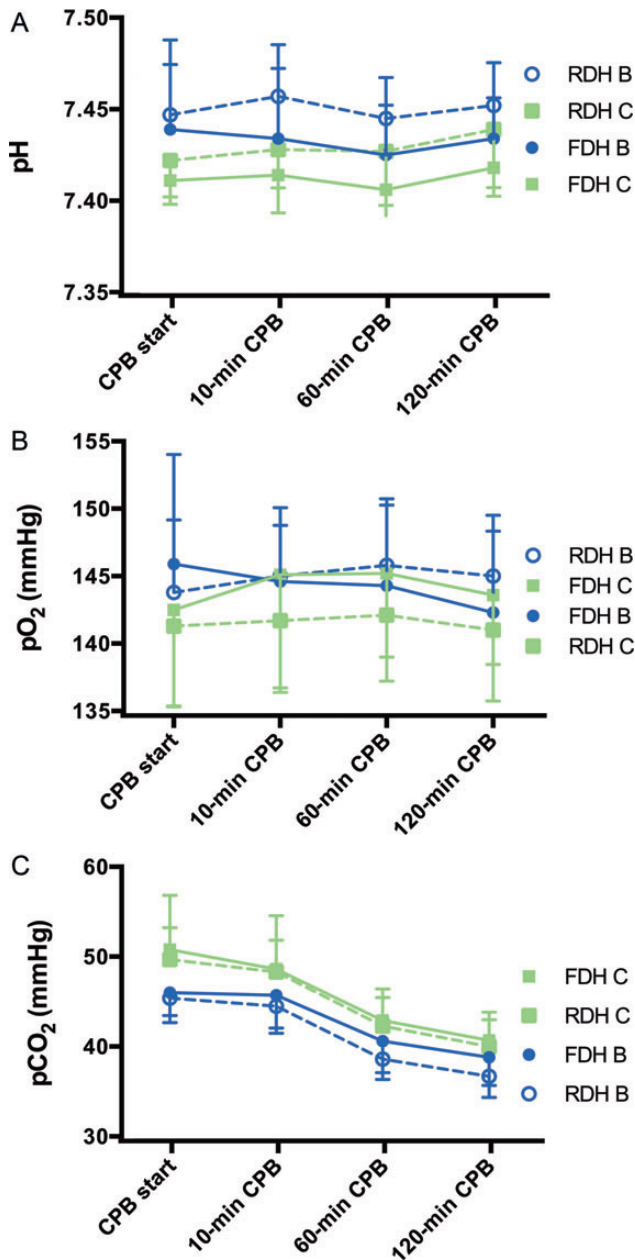


Figure 2: Blood gas parameters during *ex vivo* simulation of cardiopulmonary bypass (CPB). Data are presented as mean \pm SD. FDH-C: full-dose heparin + Carmeda® coating; FDH-B: full-dose heparin + Balance® coating; RDH-C: reduced-dose heparin + Carmeda® coating; RDH-B: reduced-dose heparin + Balance® coating. Repeated-measures ANOVA revealed an overall difference among groups for pH ($P < 0.004$), which was based on a distinction in the course of pH over time between the Balance® RDH and Carmeda® FDH groups ($P = 0.002$). The pO_2 ($P = 0.29$) and pCO_2 ($P = 0.07$) were not different among the groups.

platelet fall observed during the experiments (Fig. 3). Repeated comparisons over time did not reveal statistically significant differences among the groups for haematocrit ($P = 0.46$) and leucocytes ($P = 0.40$). There was a difference in platelet count between Balance® FDH and Carmeda® RDH ($P = 0.05$).

Activation of coagulation, leucocytes and thromboresistance

The initial activation of the coagulation contact phase was assessed based on FXII value and found to be similar to that analysed by repeated-measures ANOVA in all four groups ($P = 0.52$), as was the end split product F1.2 obtained following prothrombin

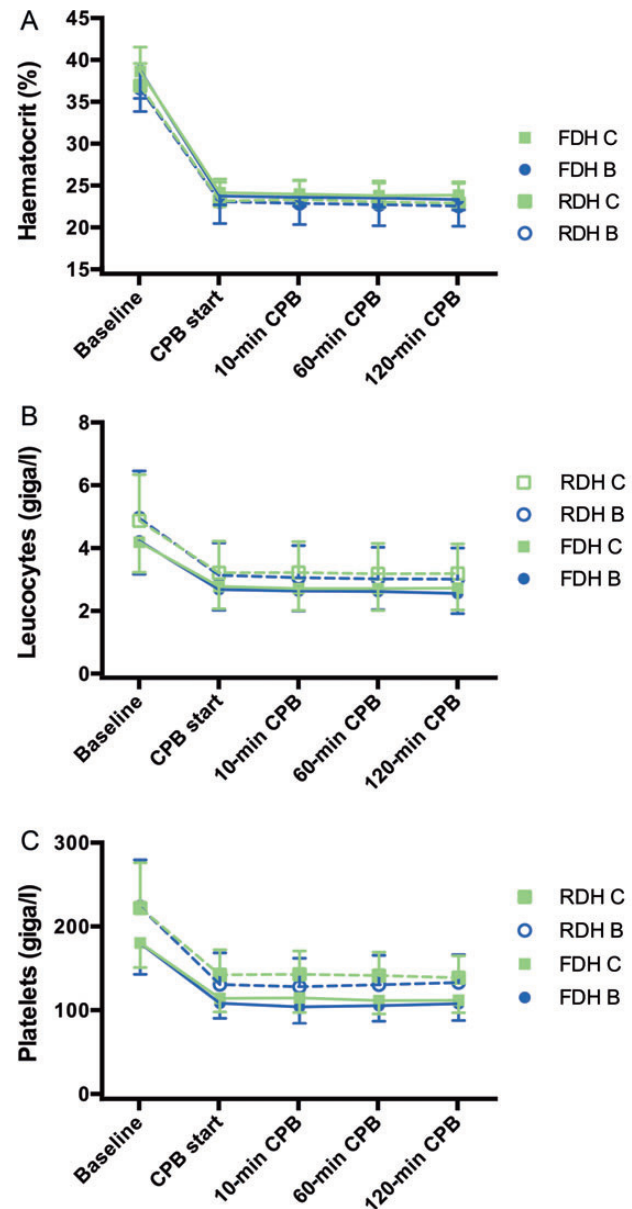


Figure 3: Blood cell counts during *ex vivo* simulation of cardiopulmonary bypass (CPB). Data are presented as mean \pm SD. FDH-C: full-dose heparin + Carmeda® coating; FDH-B: full-dose heparin + Balance® coating; RDH-C: reduced-dose heparin + Carmeda® coating; RDH-B: reduced-dose heparin + Balance® coating. Repeated comparisons over time did not reveal statistically significant differences among groups for haematocrit ($P = 0.46$) and leucocytes ($P = 0.40$). There was a difference in platelet count between Balance® FDH and Carmeda® RDH ($P = 0.05$).

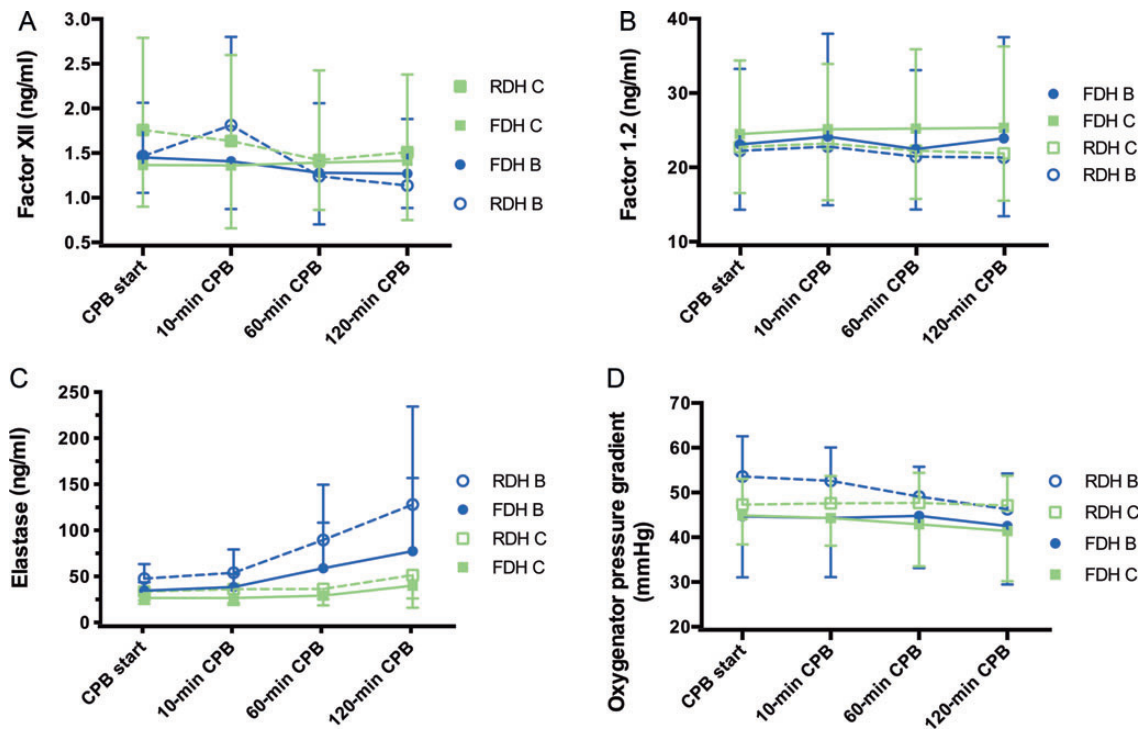


Figure 4: Activation of coagulation, leucocytes and pressure gradients across the oxygenator membrane. Data are presented as mean \pm SD. FDH-C: full-dose heparin + Carmeda[®] coating; FDH-B: full-dose heparin + Balance[®] coating; RDH-C: reduced-dose heparin + Carmeda[®] coating; RDH-B: reduced-dose heparin + Balance[®] coating. Elastase differed among groups ($P = 0.01$) based on a distinction between the Carmeda[®] FDH group and the Balance[®] RDH ($P = 0.01$). The pressure gradients among the oxygenators remained low and stable throughout ($P = 0.26$).

conversion to thrombin ($P = 0.88$) (Fig. 4). Elastase differed among the groups ($P = 0.01$) based on a distinction between the high anticoagulation regimen in the Carmeda[®] group and low anticoagulation regimen in the Balance[®] group ($P = 0.01$) (Fig. 4).

Neither the coating system nor the anticoagulation regimen proved influential during the experiments, and pressure gradients among the oxygenators remained low and stable throughout ($P = 0.26$).

Electron microscopy and scoring

Fibrin deposition and blood cell activation on oxygenators were noted to occur in small amounts (Fig. 5). No cellular adhesion or other broad deposits (Grade 6–10) were observed on analysis. All adhesion scores were low at 2 (2–3), yet similarly ranked throughout the groups, with FDH-C at 2 (2–4.25), FDH-B at 2 (2–3), RDH-C at 2 (1–3.25) and RDH-B at 2 (1.75–2.25). The Kruskal-Wallis test revealed no difference among the groups ($P = 0.74$). This therefore indicates that the two coatings have similar thromboresistance properties, even under low anticoagulation conditions (Fig. 6).

DISCUSSION

Our study demonstrated that both the Balance[®] biopassive and Bioactive Carmeda[®] coatings are thromboresistant in an *ex vivo* CPB setting, which exposes fresh human blood to artificial surfaces with no surgical environment interference. Both exhibited the same extent of contact phase activation of coagulation, as well as similar subsequent thrombin formation. Furthermore, electron microscopy detected similar levels of fibrin and cell deposits on the oxygenator ultrastructure, consistent with the stable and

normal pressure gradients measured across the oxygenator membranes throughout the procedures.

Bioactive Carmeda[®] coating is highly loaded with heparin molecules, which seep into the bloodstream, their active sequences then interacting with the blood. This surface treatment has been widely used to improve biocompatibility and clinical outcomes in routine CPB and assisted circulation, such as extracorporeal membrane oxygenation or life support [13, 14]. Even in reduced anticoagulation setting, this coating is commonly used in clinical practice [7, 8]. It could therefore be considered as a gold standard, and potentially serve as a control group to assess and compare the thromboresistance of any new coating type. This study was particularly focused on determining whether a new, non-heparin-based coating could be used safely with reduced systemic anticoagulation. This has already been successfully shown with phosphoryl-choline-coated circuits in previous studies [6, 15], yet not with other surface treatment types, such as hydrophilic polymer coating without heparin. This coating type is of particular interest given worldwide reports of severe anaphylactoid reactions caused by contaminated heparin with oversulfated chondroitin sulphate [16]. In light of this, medical regulatory authorities have recommended all manufacturers to revise their global supply chain of heparin, consequently pushing up heparin-coating manufacturing costs.

Balance[®] Biopassive coating contains negatively charged sulphonated polymers and polyethylene oxide ensuring hydrophilicity. The sulphonated groups are those that contribute to anticoagulation properties [17, 18]. This could account for the low adhesion scores observed using scanning electron microscopy (SEM) and why, even with RDH anticoagulation, no tight fibrin gel network and subsequent abnormal pressure gradients were detected across the oxygenator membranes. The fibrin gel network adheres strongly to artificial surfaces and is known to be the main cause of oxygenator dysfunction. Abnormal pressure

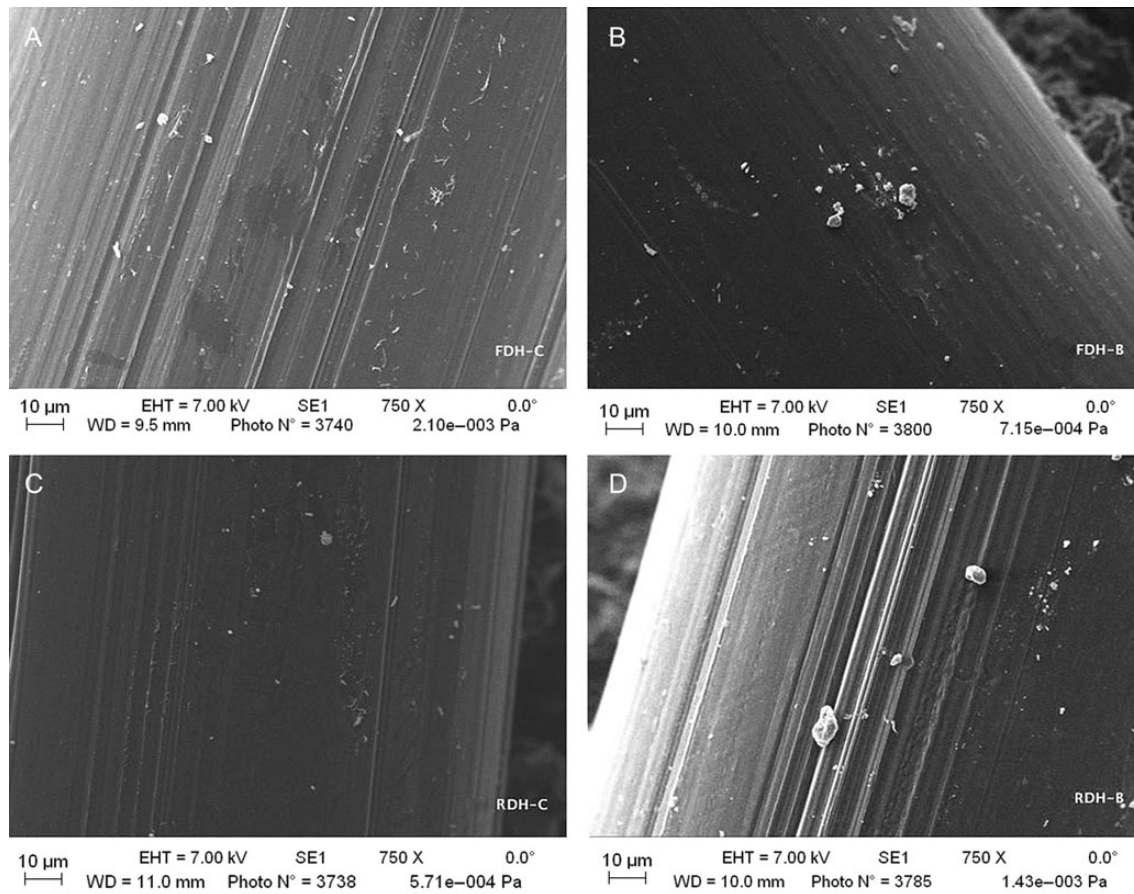


Figure 5: Scanning electron microscopy (magnification $\times 750$). An example of the mean score is illustrated for each group. (A) FDH-C: full-dose heparin + Carmeda[®] coating; (B) FDH-B: full-dose heparin + Balance[®] coating; (C) RDH-C: reduced-dose heparin + Carmeda[®] coating; (D) RDH-B: reduced-dose heparin + Balance[®] coating.

gradients when analysed as primary marker of thrombosis could be prevented by heparin coating [19, 20]. Of particular note, RDH anticoagulation with target ACT at 250 s was not associated with higher adhesion scores than those observed using an FDH anticoagulation protocol with target ACT at 500 s. Previous studies have also reported that high, rather than low, doses of heparin were associated with more granulocyte activation and white blood cell adhesion on artificial surfaces of CPB [12, 21, 22]. For this reason, we measured neutrophil activation through elastase release, which was more present using Balance[®] than using Carmeda[®] independently of the regimen of anticoagulation. Nevertheless, this was not translated by different abnormal pressure gradients across oxygenator membranes nor by different adhesion scores.

As with standard clinical practice, we used a point-of-care device to determine the adequate heparin dose required to attain target ACT according to the FDH or RDH anticoagulation protocol. Preliminary experiments and learning curve revealed several episodes of massive clotting within oxygenators before we were able to determine the adequate initial heparin dose to attain each target ACT as 1 IU/ml and 0.5 IU/ml, respectively (data not shown). This suggested that, even on contact with a biocompatible surface, this stored blood had a real capacity to clot if a minimal target ACT was not reached. Once appropriate anticoagulation, defined according to allocated group, was reached and CPB initiated, the ACTs of the Bioactive Carmeda[®] heparin-coating groups continuously increased. Lower total heparin doses when associated with Bioactive Carmeda[®] system were therefore consistent with higher ACTs than those produced with the biopassive Balance[®] circuitry. Nevertheless, no clear explanation for this shift

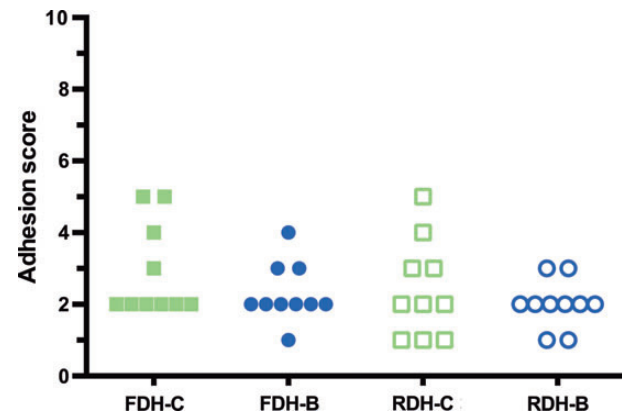


Figure 6: Adhesion score ranking among the different groups. FDH-C: full-dose heparin + Carmeda[®] coating; FDH-B: full-dose heparin + Balance[®] coating; RDH-C: reduced-dose heparin + Carmeda[®] coating; RDH-B: reduced-dose heparin + Balance[®] coating. The Kruskal-Wallis test revealed no difference among the groups ($P = 0.74$).

yet exists. End point attachment of heparin is, in truth, expected to result in a strong, covalent bond that prevents heparin from seeping through the surface during extracorporeal circulation in the presence of blood or albumin [23].

CONCLUSION

Conducted in a setting absent of surgical-related haemostatic interference, and based on target ACT levels with reduced- or full-dose

heparin, clotting processes were similar when using heparin-coated or new sulphonated polymer-coated ECC, both systems demonstrating similar thromboresistant properties. Our findings suggest that the Balance® Biosurface circuit with reduced anticoagulation may be further applied into the clinical setting. However, to date, no surface coating has been successfully proved to control the activation of the extrinsic coagulation pathway resulting from surgical procedures [24]. We must therefore stress that, in order to ensure safe clinical use of Balance Biosurface® ECCs with reduced anticoagulation protocol, the aforementioned comprehensive strategy must be implemented. This strategy includes routine use of cell saver, blood-air interface control through closed circuits and dedicated point-of-care devices for determination of adequate heparin dose.

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Conflict of interest: Christophe Baufreton and Christa Boer are invited by Medtronic to give some lectures.

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APPENDIX. CONFERENCE DISCUSSION

Dr K. Brehm (Freiburg, Germany): I have two questions regarding your presentation. The first is, don't you think that the advantage of the heparin-free coating is equalized by the need for a higher heparin dose to achieve the required ACT levels? And my second question is, if you have a look into the future, do you think a heparin-free extracorporeal circuit will be possible, which would be of great interest for extracorporeal life-support systems?

Dr Baufreton: Let me answer your second question first. I'm afraid it is not possible to think about heparin-free CPB in this kind of context, because we have seen thrombosed circuits at the time and during our learning curve, when we were not able to reach an adequate ACT. So even with coated circuits, if you don't give enough heparin, then you're going to have a clotting process. So the question is more to see whether you could safely reduce the dose of heparin with a new coating or without any kind of coating. Without any kind of coating, I don't think so. But the question is really to check what kind of safety you can get from a new coating.

Could you please repeat your first question?

Dr Brehm: Don't you think the advantage of the heparin-free coating system is equalized by the need for a higher heparin dose, as you showed, to achieve the required ACT level? Therefore you had higher heparin dosages in the bio-surface coating group?

Dr Baufreton: Honestly, I have to confess that I have no explanation for that observation. Because normally, the Carmeda® coating is known to be very strong and correctly bonded to the circuit. So if you go back to the literature, you will find that there is theoretically no leakage from that coating. So currently I have no explanation to give you to explain why we observe a shift of the ACT, despite using the lower dose of heparin during the procedure.