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The Rheological Effects of X-Coating™ with Albumin and Hetastarch on Blood during Cardiopulmonary Bypass

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Abstract: Cardiopulmonary bypass (CPB) exposes blood to artificial surfaces, resulting in mechanical damage to the formed elements of the blood. The purpose of this study was to examine the effect of poly(2-methoxyethylacrylate) coating (PMEA, X-Coating™) on coagulation and inflammation under various prime conditions. An in vitro analysis was conducted utilizing fresh whole human blood (2 units) and a CPB circuit ($n = 18$) consisting of a venous reservoir, oxygenator, and arterial filter. Nine nontreated circuits were used in a control group (CTR) and an equal number of tip-to-tip PMEA circuits for treatment (TRT). Each group was divided into three subgroups based upon prime: crystalloid, hetastarch (6%), and albumin (5%). CPB was conducted with a hematocrit 30% ± 2, temperature 37°C ± 1, and a flow of 4L/min. Samples were collected at 0, 60, 120, and 240 minute intervals. Endpoint measurements included thromboelastograph index (TI), and markers of inflammation and coagulation. The TI was significantly depressed in both groups when hetastarch was used in the prime. The TRT had significantly higher TI levels in both the crystalloid (0.3 ± 0.1 vs. -3.3±-1.2, $P < .05$) and albumin (0.6 ± 0.2 vs-3.9± -1.1. $P < .03$) subgroups compared to CTR groups. Platelet count was significantly higher in TRT as compared to CTR groups, except for both hetastarch groups. SEM demonstrated significant fibrin deposition on nontreated circuitry but little to no detection in the TRT group. In conclusion, both surface coating and prime components significantly effect coagulation, with PMEA circuits resulting in more favorable preservation of function. **Keywords:** X-coating (PMEA), protein adsorption, biocompatibility, and colloid oncotic pressure. *JECT. 2004;35:36–43*

Cardiopulmonary bypass (CPB) involves the exposure of blood to artificial surfaces resulting in mechanical damage to the formed elements of blood and activation of several biological cascades (1). These biological cascades result in the release of bradykinin, complement activation, leukocyte activation, and an increase in vascular permeability. As a result, endotoxins are released into the bloodstream (2,3). These cascades can be best visualized as an intense, whole body inflammatory reaction (4–7).

Such a whole body response increases the incidence of postoperative complications such as respiratory failure, renal dysfunction, bleeding disorders, and multiple organ failure (2,8).

During the last few decades, surface treated CPB circuits have been developed in the hopes of attenuating the systemic inflammatory response seen when blood is exposed to the foreign surface of the CPB circuit. The first of these modified circuits used heparin as a surface coating (9). Heparin-coated surfaces have been shown to reduce cellular and protein activation during CPB, resulting in decreased systemic inflammatory response (5–10).

In recent years, the focus of biocompatible surfaces has shifted to polymeric biomaterials (11). Such devices possess a number of properties that make them more physiologically compatible. Ideally, these properties include decreasing the initiation of thrombogenic phenomena, along with the initiation fibrinolysis and activation of the complement system (12). Although biocompatibility is of major relevance to the development of these polymeric perfusion biomaterials, there are other considerations to take into account. It is also mandatory for the biomaterial to be chemically and physically stable, permeable if it is to be used in a membrane and flexible if it is to be used in tubing (11).

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In accordance with these principles, a new polymeric coating has recently been developed, Poly(2-methoxyethylacrylate), or PMEA, by the Terumo Corporation under the trade name of X-Coating™ (8,13). The basis by which this coating works is through inhibition of protein adsorption to the interluminal surface of the extracorporeal circuit (13). When blood comes into contact with a foreign material, proteins are adsorbed to the surface, and the resultant protein layer determines all further blood-surface reactions (13). Protein adsorption initiates a series of cascade reactions including coagulation and inflammation. PMEA coating has been shown to reduce protein adsorption and, thus, attenuate the whole body systemic inflammatory response to the extracorporeal circuit.

A common clinical practice present in CPB procedures, is the administration of both hetastarch and albumin in prime solutions. These two components are used by clinicians in the hopes of creating a more suitable and biocompatible prime solution for CPB. Improving biocompatibility of circuits is a highly researched area, and it is anticipated that surface modified circuits will become ubiquitous in future CPB circuitry. Because artificial CPB surfaces are negatively charged, the utilization of both albumin and hetastarch in prime solutions can affect protein adsorption, which in turn, may lead to a cascade of destructive coagulation and inflammatory effects (14). The purpose of this study was to investigate the efficacy of utilizing the priming components, albumin and hetastarch, in reducing both blood activation and inflammatory response in accordance with PMEA surface treated circuits.

MATERIALS AND METHODS

Circuit Preparation

A modified in-vitro CPB circuit consisting of a hard-shell venous reservoir (Capiox SX, Terumo Cardiovascular, Ann Arbor, MI), oxygenator (Capiox SX 18, Terumo Cardiovascular, Ann Arbor, MI), Capiox arterial line filter (Terumo Cardiovascular, Ann Arbor, MI), and polyvinyl chloride tubing (Terumo Cardiovascular, Ann Arbor, MI) (Figure 1). A twin-roller pump (Stockert, Munich, Germany) was used as the blood-propelling device. Sample ports were placed from in the circuit at several locations for the measurement of transmembrane pressure and for sampling (Figure 1). Temperature was maintained at 37°C ± 1°C by the use of a heater cooler (Dual Heater Cooler, Terumo Cardiovascular, Ann Arbor, MI).

Procedure

Each circuit was primed with 1000–1200 mL of Plasmalyte A. The concentration of heparin was added to achieve a final concentration of 3 IU/mL. The prime solution was then circulated for 20 minutes, facilitating de-airing of the circuit. The anticoagulant effects of CPD were reversed with 0.2 mMol of calcium chloride. Once the blood was properly adjusted, blood priming was begun. The pump flow rate was established at 4 L/min during extracorporeal flow. A circuit pressure of 150 ± 10 mmHg was maintained via the use of an adjustable clamp placed distal to the arterial line filter.

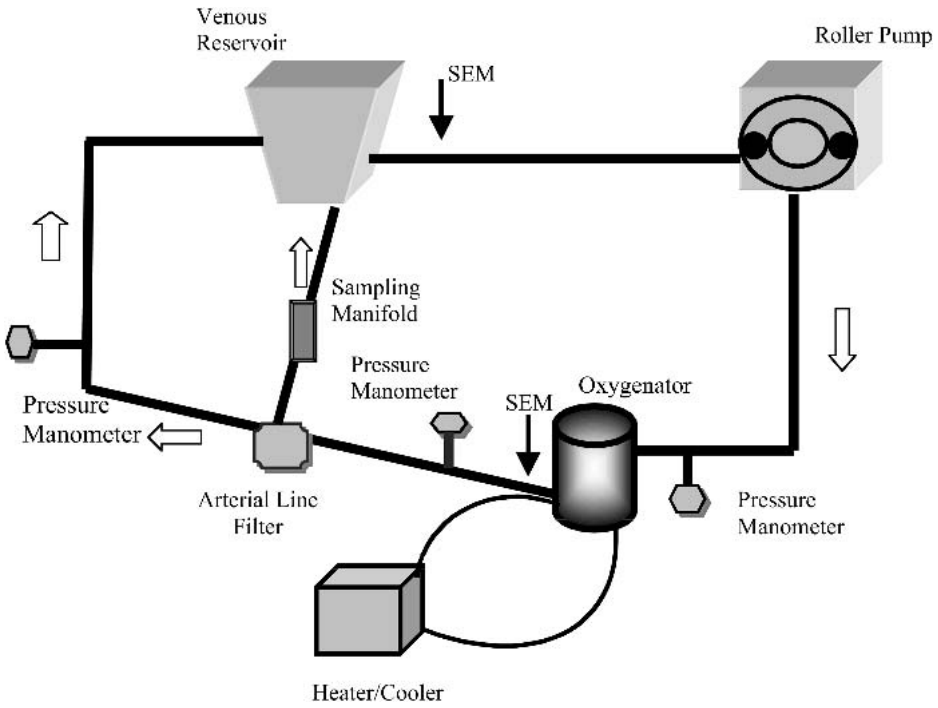

Figure 1. In vitro circuit model used for each experiment.

Blood Collection

Two units of type-specific 2-day old CPD- (citrate phosphate dextrose) treated whole human blood (450 mL/bag) were used per circuit. The blood was obtained from Interstate Blood Bank Incorporated, Memphis, TN. Blood was collected and adjusted to these values: hemoglobin content of 7 ± 1 G/dL, a base excess of 0 ± 5 mEq/L, and temperature of 37 ± 1°C. 8.4% sodium bicarbonate was used as the alkalizing agent.

Experimental Protocol

The study consisted of two separate experimental groups: PMEA (TRT) and Control (CTR). Each group consisted of nine separate circuits. The PMEA group was divided into three subgroups ($n = 3$). The subgroups had the following treatments: TRT 1 = no colloidal agent, TRT 2 = 12.5 g of Albumin (5%) per Liter prime solution, and TRT 3 = 500 mL hetastarch (6%) per Liter. The control group will consist of the same subgroups (CTR 1, CTR 2, and CTR 3) except no modification of the circuit surface.

Sample Analysis

Blood samples were drawn at five time points: 0, 5, 60, 120, and 240 minute intervals. The sample time point 0 served as the baseline and a point of comparison for the other four test points. Coagulation analysis included activated clotting time (ACT, Hemochron Response, International Technidyne Corporation, Edison, NJ), Thromboelastograph™ (TEG, Haemoscope Corporation, Skokie, IL), and platelet count (Beckman Coulter Counter, Fullerton, CA). Thrombin activation was assessed via measurement of thrombin antithrombin (TAT, Dade Berring Corporation, Deerfield, IL), and β-Thromboglobulin (Diagnostica Stago, Pasippany, NJ).

The degree of inflammatory activation was assessed by C3a (Assay Designs Inc., Ann Arbor, MI) and IL-8 (Bio-Source, Camarillo, CA) ELISA immunoassays. Scanning electron microscopy (SEM) was used to assess the conformational change of adsorbed proteins, by examining at the change in the α-helical structure of these proteins on the polymer and nonpolymer-coated surfaces (13). Two samples were taken from each circuit to be examined by SEM. The samples were cut 2.5 cm distal to the oxygenator and distal to the venous reservoir (Refer to Figure 1).

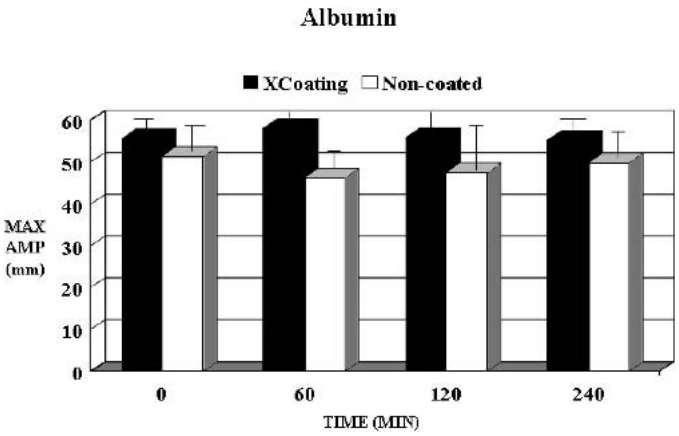

Figure 3. Albumin TEG maximum amplitude for X-Coating™ vs. noncoated circuits. $n = 3$ for each bar represented at each time point.

Statistical Analysis

All data were placed in spreadsheet form on a personal computer. Statistical analysis of the data was performed in a mixed effects model that examined the effects of coating and time on the outcome measures. Because the measurements for the experiment model were repeated over time, a repeated measures model was also used. This allows for measurement over time that can be correlated and adjusts standard errors accordingly. This model assumes that there is a linear trend over time, and a significant treatment time would indicate that the treatment has different

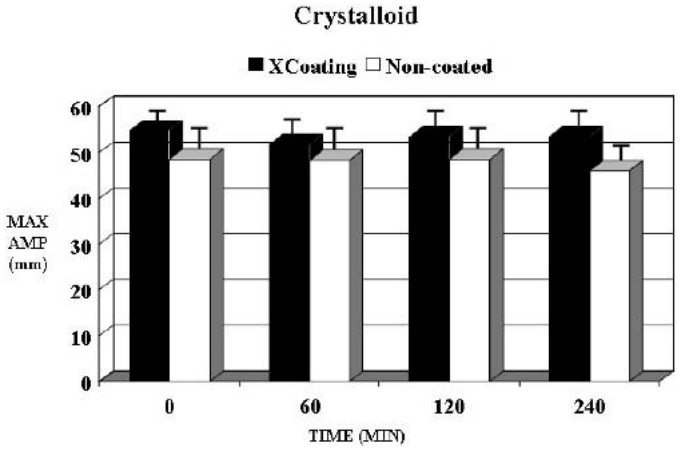

Figure 2. Crystalloid TEG maximum amplitude for X-Coating™ vs. noncoated circuits. $n = 3$ for each bar represented at each time point.

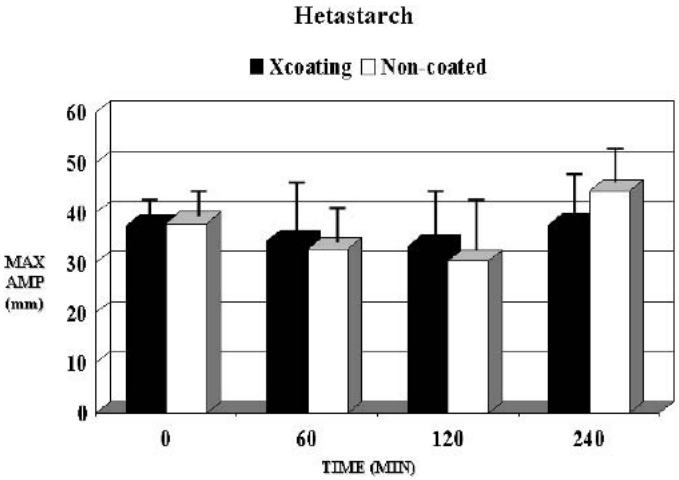

Figure 4. Hetastarch TEG maximum amplitude for X-Coating™ vs. noncoated circuits. $n = 3$ for each bar represented at each time point.

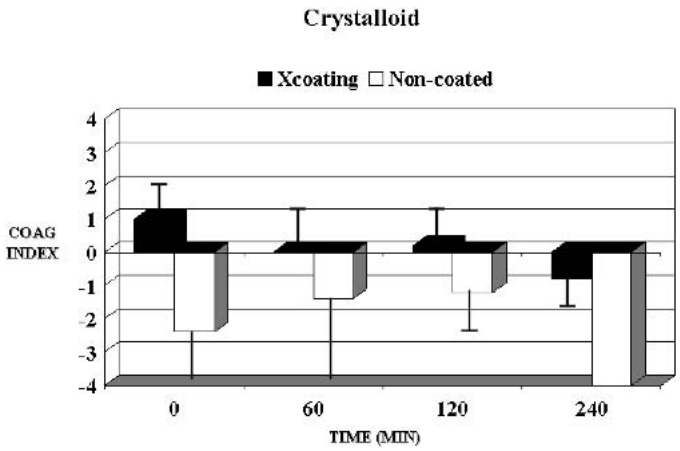

Figure 5. Crystalloid TEG coagulation index for X-Coating™ vs. non-coated circuits. $n = 3$ for each bar represented at each time point.

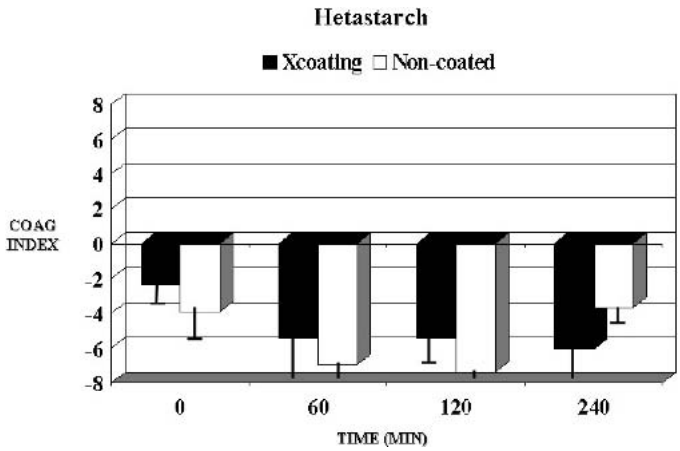

Figure 7. Hetastarch TEG coagulation index for X-Coating™ vs. non-coated circuits. $n = 3$ for each bar represented at each time point.

trends over time. The nonsignificant interaction implies that the treatments can be treated as having the same linear trend over time. Results are presented as the mean ± standard deviation of the mean. Reported P values that are less than .05 are considered statistically significant.

RESULTS

The TEG maximum amplitude showed a reduced trend for the CTR groups vs. TRT groups in crystalloid (47.4 ± 2.3, $P < .11$ vs 53.8 ± 2.3, $P < .11$) (Figure 2), albumin (49.3 ± 2.6, $P < .19$ vs. 55.3 ± 2.8, $P < .19$) (Figure 3), and hetastarch (3.7 ± 4.9, $P < .92$ vs. 35.0 ± 4.8, $P < .92$) (Figure 4). There was also a decline found in the TEG coagulation index for all the CTR groups crystalloid (–2.5 ± 1.0, $P < .11$) (Figure 5), albumin (–1.9 ± 1.1, $P < .34$) (Figure 6), and hetastarch (–5.3 ± 1.2, $P < .92$) (Figure 7) in comparison to the TRT groups crystalloid (0.3 ± 1.0, $P < .11$) (Figure 5), albumin (–0.2 ± 1.2, $P < .34$) (Figure 6), and hetastarch (–5.5 ± 1.2, $P < .92$) (Figure 7). There was significant depression in the thromoboelastograph index (TI) in both the CTR and TRT groups when hetastarch was used in the prime.

Platelet counts were found to be higher in TRT groups crystalloid (152.0 ± 21.3, $P < .20$), albumin (183.5 ± 28.4, $P < .21$), and was significant in hetastarch between 0 and 240 minutes with a P value = .017 (Figure 8) as compared to control groups crystalloid (105.9 ± 21.3, $P < .20$), albumin (112.7 ± 34.8, $P < .21$, and hetastarch, which was significant between 0 and 240 minutes with a P value = .041 (Figure 9). For the coagulation marker β-Thromboglobulin (βTG), there was a significant coating and treatment interaction ($P = 0.0007$), which indicates that the coating effect on outcome depends on which treatment (albumin, crystalloid, and hetastarch) is utilized. The CTR groups showed a significant decline of βTG where albumin was used as a prime component in comparison to crystalloid ($P < .0089$) and when crystalloid was utilized in comparison to Hetastarch ($P < .031$) (Figure 10). TRT groups showed a significant depression of βTG where

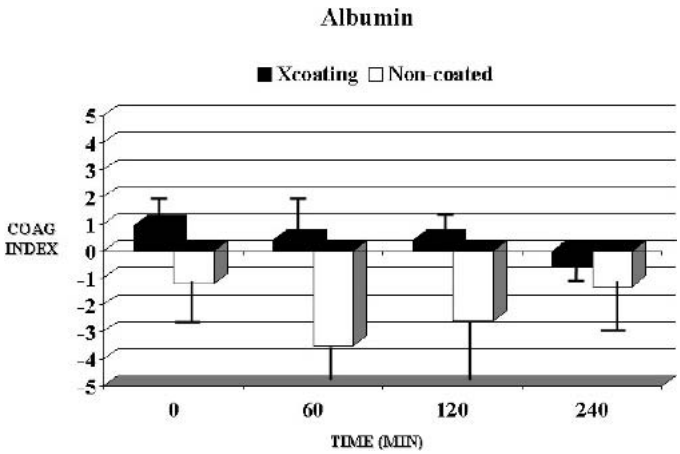

Figure 6. Albumin TEG coagulation index for X-Coating™ vs. non-coated circuits. $n = 3$ for each bar represented at each time point.

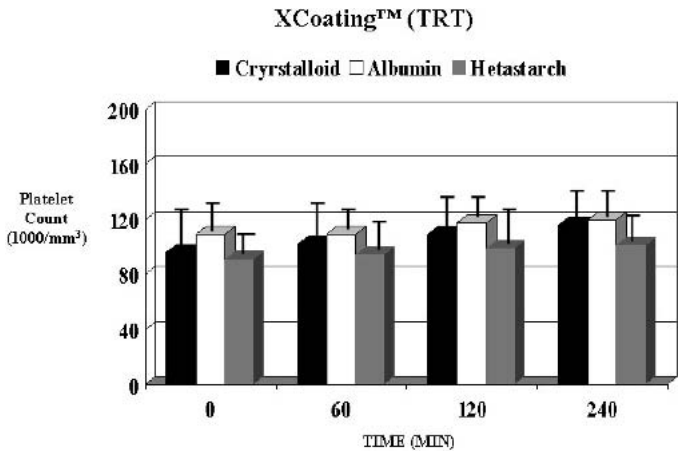

Figure 8. X-coating™ platelet count for each subgroup: Crystalloid, albumin, hetastarch. $n = 3$ for each bar represented at each time point.

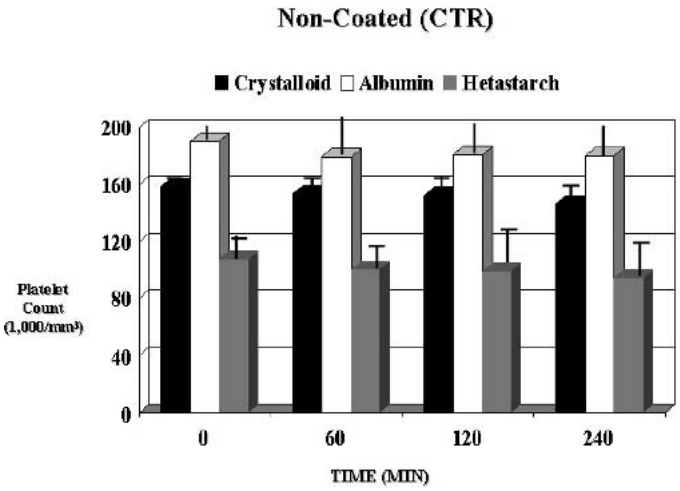

Figure 9. Noncoated platelet count for each subgroup: Crystalloid, albumin, hetastarch. $n = 3$ for each bar represented at each time point.

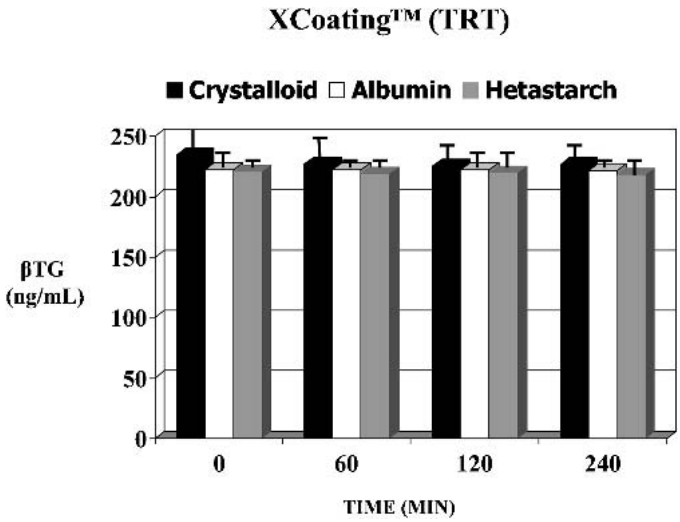

Figure 11. X-coating™ (TRT) circuits β-thromboglobulin concentrations for each subgroup: Crystalloid, albumin, hetastarch. $n = 3$ for each bar represented at each time point.

albumin was used as a prime component in comparison to crystalloid ($P < .0089$) and when crystalloid was utilized in comparison to Hetastarch ($P < .0013$) (Figure 11). As for the thrombin antithrombin (TAT) assays, there was no significant reduction of TAT between the CTR subgroups albumin, crystalloid and hetastarch ($P > .05$) (Figure 12) in comparison to TRT groups albumin, crystalloid, and hetastarch ($P > .05$) (Figure 13).

The inflammatory markers Interleukin-8 (IL-8) and C3a showed that there was a significant coating and treatment interaction ($P = .0002$ for IL-8 and $P = .0030$ for C3a), which indicates that the coating effect on outcome depends on which treatment (albumin, crystalloid, and hetastarch) is utilized. The CTR groups showed a significant decline of IL-8 where albumin was used as a prime component in comparison to crystalloid ($P < .0001$) and when crystalloid was utilized in comparison to hetastarch ($P < .0001$) (Figure 14). TRT groups showed a significant depression of IL-8 where albumin was used as a prime component in comparison to crystalloid ($P < .038$), when crystalloid was utilized in comparison to hetastarch ($P < .0002$), and when albumin was compared to hetastarch ($P < .0001$) (Figure 15). The CTR groups showed a significant decline of C3a where albumin was used as a prime component in comparison to crystalloid ($P < .0014$) and when albumin was utilized in comparison to hetastarch ($P < .0021$) (Figure 16). TRT groups showed a significant depression of C3a only when utilized in comparison to crys-

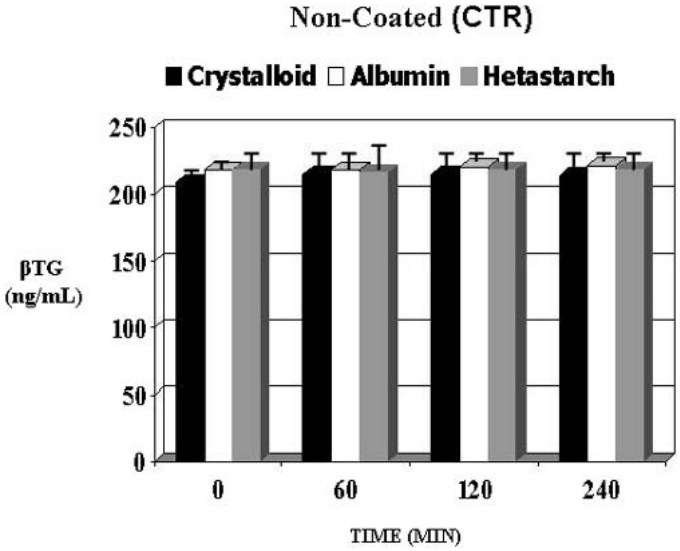

Figure 10. Non-coated (CTR) circuits β-thromboglobulin concentrations for each subgroup: Crystalloid, albumin, hetastarch. $n = 3$ for each bar represented at each time point.

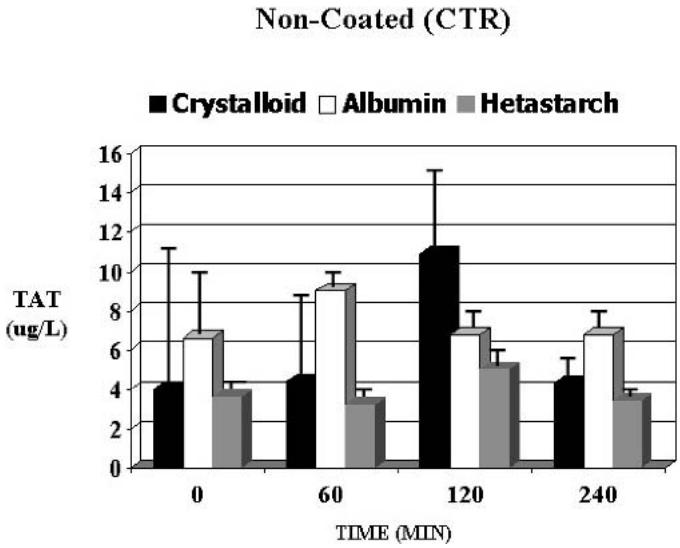

Figure 12. Non-coated (CTR) circuits thrombin antithrombin complex concentrations for each subgroup: Crystalloid, albumin, hetastarch. $n = 3$ for each bar represented at each time point.

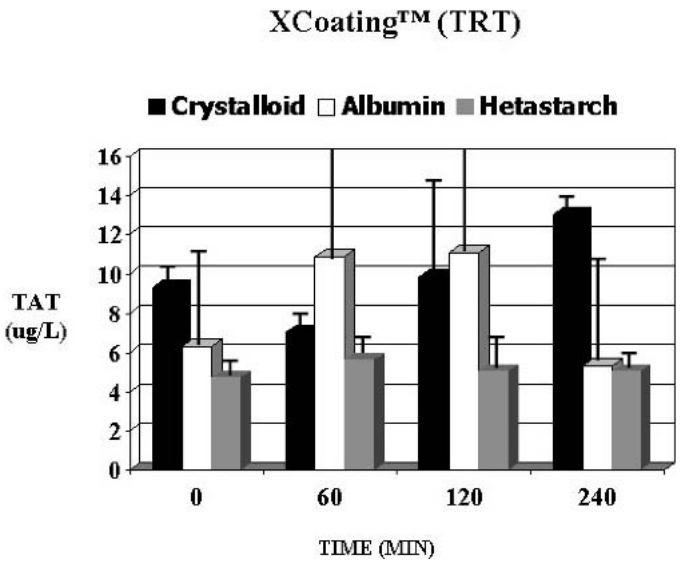

Figure 13. X-coating™ (TRT) circuits thrombin antithrombin complex concentrations for each subgroup: Crystalloid, albumin, hetastarch. *n* = 3 for each bar represented at each time point.

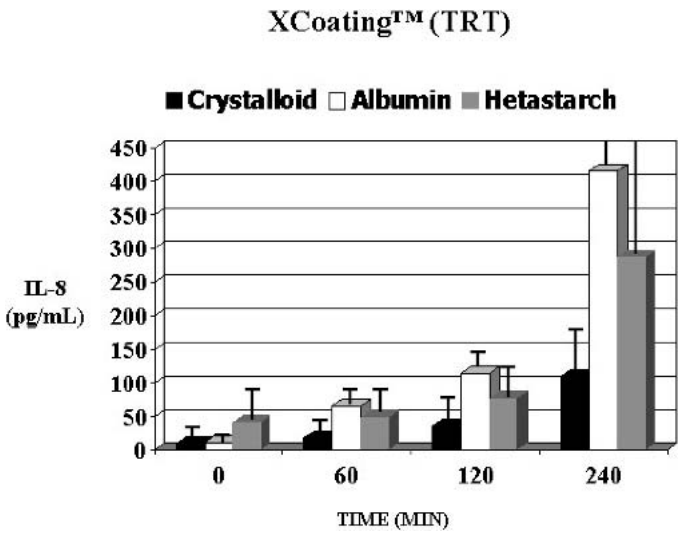

Figure 15. X-coating™ (TRT) circuits interleukin-8 concentrations for each subgroup: Crystalloid, albumin, hetastarch. *n* = 3 for each bar represented at each time point.

talloid ($P < .05$) (Figure 17). SEM detected the presence of fibrin deposition on the CTR groups (Figure 18) for the three subgroups of crystalloid, albumin, and hetastarch. There was no evidence of fibrin deposition (Figure 19), as seen with the CTR, on any of the same three subgroups.

DISCUSSION

Focus on making cardiopulmonary bypass circuits more biocompatible has encouraged the technology of creating new surface treated circuitry (11). Several studies show that exposure to foreign surfaces leads to cascades of inflammatory and coagulation responses that adversely effect blood components (2,4–8). Some of the first advances in coated surfaces found that with the use of heparin-treated circuits, there was a reduction of postoperative blood loss, complement activation, fibrin deposition, platelet activation, and degranulation along with thrombogenicity (5–10).

Progressive development in treated circuits has lead to the creation of even more physiologically compatible surfaces (11–13). X-Coating™ is an example of such a surface treatment, which has a hydrophobic background and hydrophilic surface allowing for the coating to swell and create a molecular mesh (2). Proteins are, thus, allowed to maintain their native conformation and move freely between the boundary layer and the bloodstream as in nor-

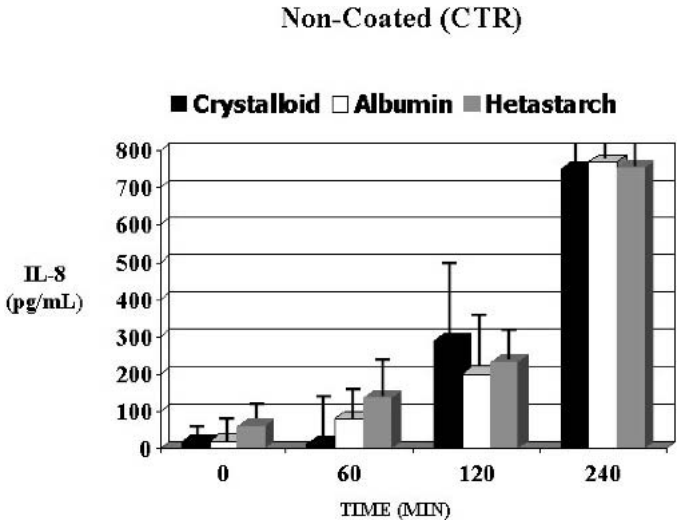

Figure 14. Non-coated (CTR) circuits interleukin-8 concentrations for each subgroup: Crystalloid, albumin, hetastarch. *n* = 3 for each bar represented at each time point.

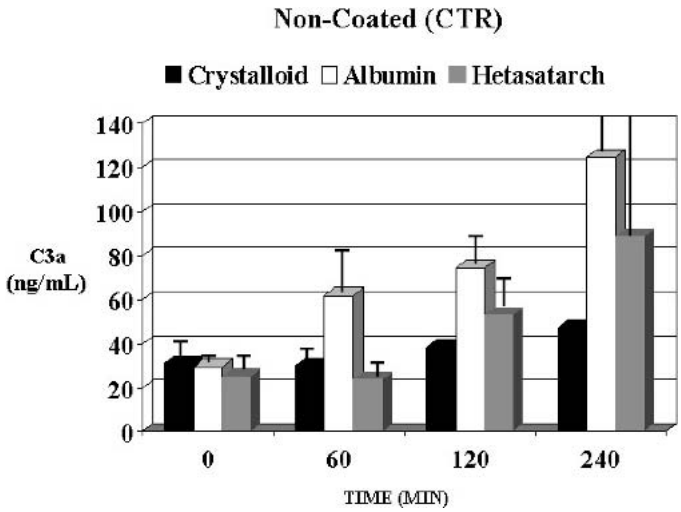

Figure 16. Non-coated (CTR) circuits complement-C3a concentrations for each subgroup: Crystalloid, albumin, hetastarch. *n* = 3 for each bar represented at each time point.

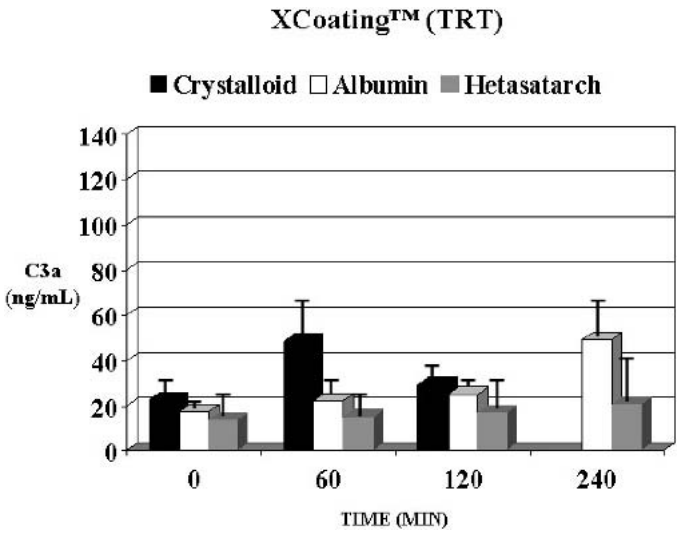

Figure 17. X-coating™ (TRT) circuits complement-C3a concentrations for each subgroup: Crystalloid, albumin, hetastarch. *n* = 3 for each bar represented at each time point.

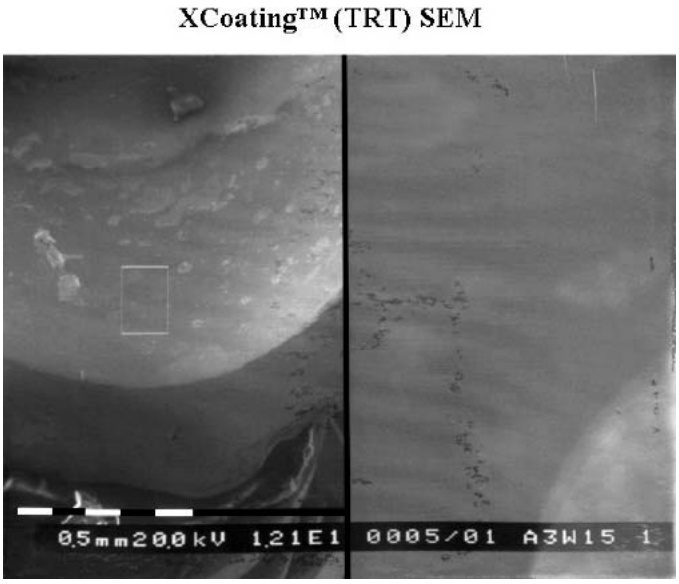

Figure 19. SEM X-coating™ (TRT) circuit tubing sample (2.5 cm) with fibrin deposition. 12× magnification.

mal circulation. Therefore, proteins do not become denatured, and platelets will not adhere to the surface.

Another measure of ensuring better biocompatibility is the administration of priming components in addition to crystalloid to help make effects of CPB less deleterious on blood and outcomes (15–17). A common solution added to prime is albumin, a natural colloid plasma component that has been shown to improve post-operative patient outcomes and decrease morbidity associated with CPB (18). According to the product insert, this protein accounts for 70–80% of the colloid oncotic pressure of plasma, and it is important in regulating the volume of circulating blood. Albumin serves both to coat the CPB circuit along with acting as a plasma expander (14–18). In CPB, it plays a role in maintaining colloid oncotic pressure as well as reducing platelet adhesion and decreasing patient postoperative morbidity (15–18,19). Studies suggest that albumin may be of benefit in reducing postoperative bleeding, low cardiac output, pulmonary dysfunction, renal dysfunction, and congestive heart failure (15,16,18). Therefore, albumin has profound effects on COP, plasma volume expansion, and surface coating capabilities, which clearly impacts the adequacy of perfusion (14,20).

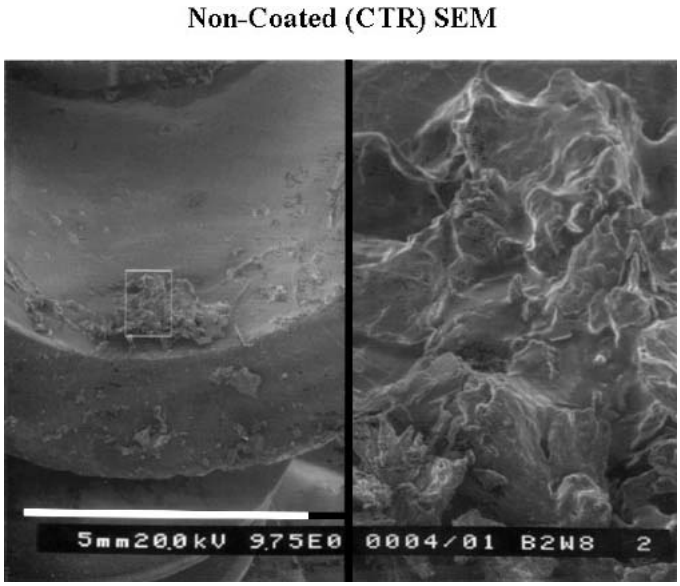

Figure 18. SEM Non-coated (CTR) circuit tubing sample (2.5 cm) with fibrin deposition. 9× magnification.

Another example of a plasma expander that can be used in CPB is synthetic hetastarch (6% hydroxyethyl starch). Hetastarch has been used as an alternative to colloid solutions, such as albumin, because of several similar characteristics, which include: lower cost, similar efficiency, better availability, longer shelf life, longer duration of action, and reduced infectious risk (15,19,21,22). The use of hetastarch as a volume expander has been shown to preserve hemodynamics similar to human albumin (18). Hetastarch contains hydrolyzed polysaccharides, which are rapidly excreted by the kidneys and has a maximum dosing of 20 mL/kg per 24-h period (14,15). Although, recent studies have shown that hetastarch administration does impair hemostasis and may increase bleeding and transfusion requirements (15,21–24).

Efforts of utilizing components such surface coating and different prime solutions are geared toward making CPB more biocompatible and less damaging to blood components (25). The circuit models used in this study combined the use of both treated circuits with three important prime solutions: crystalloid, albumin, and hetastarch to examine their effects upon blood. This study demonstrated that

there was a true relationship between prime components and coagulation potential. Of the three components albumin had the greatest coagulation preservation in comparison to crystalloid and hetastarch. This was true for both X-Coated™ TRT and noncoated CTR groups. X-Coating™ was also shown to preserve platelet count and function best along with preventing the activation and deposition of fibrin.

In summary, surface coating and prime components do have an impact on coagulation and inflammatory reactions when blood is exposed to the foreign surfaces of the cardiopulmonary bypass circuit. The use of X-Coating™ will improve biocompatibility and when used in conjunction with albumin results in decreased cellular activation and enhances biocompatibility. Most results were not statistically significant, which was attributed to the limitation of repeated numbers of circuits and trial runs.

ACKNOWLEDGMENTS

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