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***In Vivo* Evaluation of a New Surfactant Polymer Coating Mimicking the Glycocalyx of Endothelial Cells**

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Abstract

The purpose of the current study was to demonstrate that a proprietary surfactant polymer coating does not adversely affect the hemodynamic performance of cardiopulmonary bypass (CPB) or gas exchange in oxygenators. The new coating was applied to a CPB circuit including cannulae, reservoir, oxygenator, and blood pump implanted into 12 pigs, divided into groups with either coated or noncoated pumps. CPB flow was maintained at a fixed level of approximately 2.4 L/min for 6 hrs with full heparinization. Hemodynamic data and pump performance were recorded every hour, and blood samples were taken every 2 hrs. After sacrifice, the CPB circuit and major organs were macroscopically examined. There was no significant difference in the oxygen transfer rate between the two groups. The coating did not adversely affect oxygenator inlet or outlet pressures. There was no significant difference between the two groups in microthrombi seen in the oxygenators. No thromboemboli were noted in the major organs on gross or histologic examination. In conclusion, this new surfactant polymer coating did not decrease gas exchange performance and its biocompatibility evaluations revealed no differences between coated and noncoated groups under aggressive heparin use.

Keywords

Coating; glycocalyx; biocompatibility; cardiopulmonary bypass

Circulatory and respiratory assist devices, such as cardiopulmonary bypass (CPB) circuits, ventricular assist devices, and extracorporeal membrane oxygenators, are in common use in cardiac surgery and postoperatively to support patients with impaired cardiac function.¹ Although these devices have been shown to be effective in supporting perfusion and oxygenation, biocompatibility issues have arisen as a result of the patient's blood contacting the device's surfaces. These concerns include activation of blood proteolytic systems (such

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as coagulation, complement, and fibrinolysis) and cellular blood components (such as platelets and leukocytes).² Postsurgical complications from this biocompatibility response include activation of an anaphylactic reaction, pulmonary and renal dysfunction, cerebral problems, and coagulopathy, all of which increase risks to the patient, extend postsurgical recovery time, and add to the overall cost of treatment.³

Blood-compatible coatings have been widely investigated and developed to prevent adverse effects of blood-contacting foreign surfaces. The majority of commercial coatings are heparin based. Several reports in the literature, however, indicate that even when heparin-coated CPB systems are used, systemic heparinization is still required to prevent thromboembolic complications.

A novel and promising type of biomaterial surface passivation (biolization) is a surfactant polymer (SP) coating, investigated by Holland and colleagues in 2004.⁴ The SP molecule consists of a polymeric backbone chain having two types of functional groups attached to it. The hydrophobic group provides SP adhesion to the foreign surface, and the blood-compatible hydrophilic group “faces” the blood flow. The chemistry and structure of the hydrophilic group mimics the network of membrane-bound proteoglycans and glycoproteins covering the endothelial lumen of blood vessels, referred to as the endothelial glycocalyx, improving compatibility with blood. The most important practical advantage of this SP coating over other biolized coatings is its low cost and the ease with which it is applied to surfaces. The SP coating forms a self-assembling monolayer with a coating thickness of approximately 4 μm . These factors make it a potential biolization material for coating the majority of the existing cardiac assist devices, oxygenators, CPB tubing and reservoirs without the need for design changes. The purpose of this study was to demonstrate that the SP coating does not adversely affect the hemodynamic performance of CPB or gas exchange in oxygenators.

MATERIALS AND METHODS

Surfactant Polymer Coating

The synthesis of these SPs was performed according to the methods described by Holland and colleagues.⁴ Briefly, the process consists of two main stages: (1) It is first necessary to prepare three subcomponents of the SP molecule: dextran lactone, poly(vinylamine), and N-(hexanoyloxy)succinimide. (2) The next step is the final synthesis of the SP molecule, consisting of a poly(vinylamine) backbone, to which dextran lactone hydrophilic groups and hexanoyl hydrophobic groups are attached.

Blood-Compatible Coating Method

The CPB circuit tested consisted of a BPX-80 Bio-Pump® Plus Centrifugal Blood Pump, Affinity® NT oxygenator, 20 Fr arterial cannula and a 28–36 Fr venous cannula (Medtronic, Minneapolis, MN). Prior to coating, the pump, oxygenator, and cannulae were cleaned using a peristaltic pump and tubing in a 1:10 mixture of isopropyl alcohol and deionized water for 10 min, followed by rinsing with deionized water to remove the isopropyl alcohol. The components were then rinsed again for 10 min in deionized water and dried using filtered compressed air for 1 hr. The coating was applied by continuous circulation of the SP water solution (0.15% w/v) through the components at 40°C for 5 hrs; this length of time was chosen based on our previous data, which showed that 5 hrs was enough to coat any surface, independent of the contact angle [unpublished data]. After coating of the components was completed, the solution was drained, and the pump was rinsed twice with deionized water in 3-min cycles and dried using filtered compressed air for 1 hr. All components were then

sterilized by ethylene oxide gas. The noncoated control components were used as supplied by Medtronic in ethylene oxide sterilized packages, without further reprocessing.

Acute *In Vivo* Study

This acute study was performed using 12 pigs (Yorkshire mix, 57.4 ± 7.8 kg; Fanning Farms, Howe, IN). The study was approved by the Cleveland Clinic's Institutional Animal Care and Use Committee, and all animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council. The animals were quarantined for more than a week prior to the study.

The animals were placed in the supine position under general anesthesia with isoflurane (1.0–2.5%). A median sternotomy was performed. Systemic arterial pressure (AP), left atrial pressure (LAP), and central venous pressure (CVP), and the oxygenator's inlet and outlet pressures were monitored using fluid-filled lines. Blood gas samples were taken from the inlet and outlet sampling ports of the oxygenator after initiation of CPB and every 2 hrs following that initial blood draw. Complete systemic heparinization (3 mg/kg IV heparin) was achieved, and then the CPB arterial cannula (20 Fr) and a venous cannula (28–36 Fr) were inserted into the ascending aorta and the right atrium, respectively. The activated clotting time was maintained over 450 s throughout the CPB period. A 20-mm Transonic perivascular flow probe (Transonic Systems Inc., Ithaca, NY) was placed around the pulmonary artery to monitor the native pulmonary arterial flow. The CPB pump flow was recorded from the BPX-80 Bio-Pump console.

Hemodynamics and blood gases were recorded 10 min after initiation of CPB and every hour thereafter. Blood sampling to obtain a complete blood count and comprehensive metabolic panel was performed 10 min after initiation of CPB and every 2 hrs following that initial blood draw. Hemodynamic data included heart rate, AP, LAP, CVP, oxygenator inlet and outlet pressures, CPB pump flow, and native pulmonary arterial flow.

After completion of 6 hrs of CPB, the animal was sacrificed, and the pump circuit and oxygenator were assessed macroscopically. Major organs were examined for thromboembolism macroscopically and also via serial 1.5-cm sectioning. Specimens for further histological analysis were taken from the lung, kidney, liver, spleen, adrenal, and pancreas. All fixations were performed with formalin.

Measurement of Oxygen Transfer Rate

To measure the oxygen transfer rate, blood gas samples were taken from the oxygenator inlet and outlet ports 10 min after initiation of CPB and every hour following that for a total of 6 hrs to compare coated vs. uncoated oxygenator function under relatively steady-state conditions. The gas flow throughout the experiment was kept at a V/Q ratio (V = gas flow rate; Q = blood flow rate) of approximately 1.0 using 100% oxygen. The oxygen transfer rate (mL O₂/min) was calculated by the following standard formulae:

$$\begin{aligned} \text{CaO}_2 &= (\text{Hb} \times 1.34 \text{ mL O}_2/\text{g Hb} \times \text{arterial O}_2 \text{ sat } (\%)/100) + (\text{PaO}_2 \times 0.003 \text{ mL O}_2/\text{mm Hg/dL}) \\ \text{CvO}_2 &= (\text{Hb} \times 1.34 \text{ mL O}_2/\text{g Hb} \times \text{venous O}_2 \text{ sat } (\%)/100) + (\text{PvO}_2 \times 0.003 \text{ mL O}_2/\text{mm Hg/dL}) \\ \text{O}_2 \text{ transfer rate (mL/min)} &= (\text{CaO}_2 - \text{CvO}_2) \times 10 \times \text{blood flow rate (L/min)}; \end{aligned}$$

where CaO₂ = arterial oxygen content (mL O₂/100 mL), sat = saturation, CvO₂ = venous oxygen content (mL O₂/100 mL), Hb = hemoglobin (g/dL), and PaO₂/PvO₂ = arterial/venous oxygen partial pressure (mm Hg).

Statistical Analysis

All data are presented as group means $\pm$ standard deviation. The SPSS statistical software program (SPSS for Windows, SPSS inc., Chicago, IL) was used to analyze the data. An unpaired *t* test was performed to compare values between the coated and noncoated groups at each data point. A value of $p < 0.05$ was considered statistically significant.

RESULTS

There was no significant difference in oxygen transfer rate between the coated vs. noncoated groups at any of the times (10 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, and 6 hrs) when data was recorded after the initiation of CPB (Table 1). CPB flow was maintained at a fixed level (noncoated, 2.5 ± 0.2 L/min; coated, 2.4 ± 0.2 L/min) for 6 hrs and did not show any significant differences between groups. The PA flow was essentially zero at all the recorded data points (Table 1). The inflow, outflow, and differential between inlet and outlet pressures of the oxygenator were not significantly affected by the coating (Table 2). The plasma free hemoglobin, platelet, and lactate levels showed no significant difference between the two groups at 10 min, 2 hrs, 4 hrs, and 6 hrs after initiation of CPB (Table 3). There was no significant change in the lactate level (noncoated, 3.0 ± 1.4 mmol/L; coated, 2.8 ± 1.2 mmol/L; $p = 0.73$). Hemodynamic data including heart rate, AP, LAP, and CVP show no significant difference between the groups except for the LAP data at 10 min (Table 4).

No thromboemboli were noted in the major organs on gross inspection, 1.5 cm serial sectioning or histologic examination. There was no clot formation in the heart. The CPB circuit, including cannulae, reservoir, and oxygenator, showed no adverse macroscopic findings (e.g., blood clots, signs of coating delamination, or discoloration). In two cases in the coated group, a white object (5×6 mm and 5×4 mm) was found attached to the BPX-80 Bio-Pump head surface; in each case, the object was confirmed to be a piece of the white tubing used to clean the circuit parts.

COMMENTS

Our findings from this pilot study lead us to conclude that this new SP coating did not adversely affect CPB under full heparinization. The most important aspect of the SP coating is that it is inexpensive and can be applied to any blood-contacting device, in full or in part. The design and configuration of the device would not need to be changed for this type of coating to be employed, and it can be applied before or after final assembly of the device, dramatically decreasing coating costs and increasing its utility in a wide range of clinical applications.

Previously, the stability of the coating was validated when photoelectron spectroscopy (XPS) analysis for nitrogen content was performed on freshly coated pumps and after their exposure to simulated CPB flow of 2.0 L/min for 4 hrs in a mock circulation loop using phosphate-buffered saline. As there is no nitrogen in the polycarbonate base tubing, the nitrogen content detected by XPS analysis of the coated surface can only come from the polyvinyl amine backbone chain of the coating. The freshly coated pumps showed an average nitrogen content of 5.5%, which dropped to 5.1% after exposure to the simulated CPB flow. Since the SP coating thickness is approximately 4 μ m, and the depth of XPS analysis is in the range of 5–10 μ m, we are confident that approximately 90% of the initial coating concentration was retained.

One negative finding in this *in vivo* study included a clear downward trend in circulating platelets with time in both coated and noncoated groups; however, there was no significant

difference in platelet counts between the groups. The only statistically significant difference between the groups for all of the recorded hemodynamics throughout the 6-hr runs occurred at the 10-min post-CPB reading, where LAP was 7 mm Hg for the coated circuit vs. 3 mm Hg for the noncoated one. Regarding the statistical analysis, since we used an unpaired *t* test and had 60 parameters tested, there is a possibility of having both type I and type II errors. White foreign objects found attached to the BPX-80 Bio-Pump head surface in two cases were confirmed to be pieces of the tubing used to clean the circuit parts after coating. Based on this finding, we are studying ways to improve the method used to clean these circuits.

With the success of long-term circulatory assist devices, new blood-compatible coatings have been increasingly investigated to prevent any adverse effects from blood-contacting foreign surfaces.^{5,6} Circulatory assist devices are rapidly becoming a viable therapeutic option for end-stage heart failure and are being increasingly used in elderly patients.⁷ Even with the reported significant improvements in the new continuous-flow ventricular assist devices over their pulsatile predecessors, thromboembolism and bleeding associated with anticoagulation use remain two of the major complications associated with these devices.⁸ It is hoped that better biocompatible coatings, such as the SP type coating, will further decrease these adverse events.

A limitation of this study was the fact that the SP coating was applied only to a CPB circuit for study durations limited to only 6 hrs. Additional studies should be conducted using a full SP coating for longer durations, such as those typically encountered in extracorporeal membrane oxygenation or ventricular assist device applications. Comparative evaluations of SP-coated CPB circuits and implanted blood-contacting devices without systemic heparinization should also be conducted.

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Table 1

Oxygen transfer rate, cardiopulmonary bypass (CPB) flow, pulmonary arterial (PA) flow, the ratio of PA flow to CPB flow

Parameter	Data at Time After CPB						
Oxygen transfer rate	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (mL/min)	338 ± 41	351 ± 24	384 ± 45	382 ± 45	397 ± 49	375 ± 68	396 ± 55
Coated (mL/min)	361 ± 41	357 ± 87	390 ± 55	353 ± 76	351 ± 40	365 ± 50	351 ± 36
<i>p</i> value	0.35	0.88	0.82	0.44	0.10	0.78	0.12
CPB flow	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (L/min)	2.5 ± 0.2	2.4 ± 0.2	2.3 ± 0.2	2.4 ± 0.2	2.4 ± 0.3	2.4 ± 0.2	2.5 ± 0.2
Coated (L/min)	2.3 ± 0.2	2.4 ± 0.2	2.4 ± 0.2	2.4 ± 0.2	2.5 ± 0.3	2.4 ± 0.2	2.5 ± 0.2
<i>p</i> value	0.19	1.00	0.37	0.71	0.80	0.97	0.99
PA flow	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (L/min)	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	0.0 ± 0.1	0.1 ± 0.2	0.0 ± 0.1
Coated (L/min)	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1
PA/CPB Flow Ratio	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.0
Coated	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

CPB, cardiopulmonary bypass; PA, pulmonary artery.

Table 2

Oxygenator inflow, outflow, and differential pressures

Parameter	Data at Time After CPB						
Inflow pressure	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (mm Hg)	169 ± 22	167 ± 17	168 ± 11	165 ± 13	166 ± 15	166 ± 14	168 ± 11
Coated (mm Hg)	171 ± 29	186 ± 56	169 ± 20	169 ± 20	168 ± 22	173 ± 17	168 ± 18
<i>p</i> value	0.87	0.43	0.92	0.72	0.86	0.48	0.98
Outflow pressure	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (mm Hg)	118 ± 18	127 ± 19	128 ± 16	126 ± 19	133 ± 25	132 ± 21	132 ± 20
Coated (mm Hg)	108 ± 32	112 ± 29	113 ± 32	118 ± 34	117 ± 32	119 ± 28	115 ± 32
<i>p</i> value	0.51	0.33	0.31	0.62	0.36	0.41	0.29
Differential pressure (Inflow – Outflow)	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (mm Hg)	50 ± 19	40 ± 19	40 ± 17	40 ± 15	33 ± 15	35 ± 14	36 ± 13
Coated (mm Hg)	63 ± 21	74 ± 36	57 ± 16	51 ± 21	50 ± 21	54 ± 25	53 ± 23
<i>p</i> value	0.29	0.07	0.11	0.29	0.12	0.13	0.14

CPB, cardiopulmonary bypass.

Table 3

Plasma free hemoglobin, lactate values, platelet and white blood cell counts

Parameter	Data at Time After CPB			
Plasma Free Hgb	10 min	2 hrs	4 hrs	6 hrs
Noncoated (mg/dL)	6.1 ± 9.2	18.1 ± 21.5	21.4 ± 23.0	27.6 ± 25.7
Coated (mg/dL)	4.8 ± 5.2	14.1 ± 7.3	27.4 ± 21.5	30.3 ± 16.9
<i>p</i> value	0.77	0.68	0.65	0.84
Lactate	10 min	2 hrs	4 hrs	6 hrs
Noncoated (mmol/L)	4.1 ± 2.5	3.2 ± 1.2	2.4 ± 0.7	3.0 ± 1.2
Coated (mmol/L)	2.6 ± 0.8	3.3 ± 1.9	2.5 ± 1.0	2.5 ± 0.9
<i>p</i> value	0.22	0.86	0.74	0.46
Platelet Count	10 min	2 hrs	4 hrs	6 hrs
Noncoated (10 ³ /μL)	289 ± 48	204 ± 72	164 ± 72	135 ± 82
Coated (10 ³ /μL)	258 ± 96	151 ± 29	117 ± 27	103 ± 16
<i>p</i> value	0.58	0.18	0.17	0.37
White Blood Cell Count	10 min	2 hrs	4 hrs	6 hrs
Noncoated (10 ³ /μL)	19.1 ± 9.4	19.7 ± 6.0	25.7 ± 5.3	31.0 ± 4.2
Coated (10 ³ /μL)	20.0 ± 9.0	15.1 ± 6.6	18.8 ± 10.1	24.2 ± 11.1
<i>p</i> value	0.88	0.23	0.17	0.19

CPB, cardiopulmonary bypass.

Table 4

Hemodynamic data

Parameter	Data at Time After CPB						
Heart rate	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Non-coated (bpm)	96 ± 14	94 ± 22	97 ± 16	99 ± 16	107 ± 26	102 ± 21	100 ± 12
Coated (bpm)	107 ± 23	103 ± 17	99 ± 16	92 ± 11	84 ± 15	97 ± 11	93 ± 16
<i>p</i> value	0.32	0.48	0.87	0.40	0.09	0.63	0.42
mAP	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (mm Hg)	64 ± 18	59 ± 10	63 ± 9	58 ± 8	62 ± 15	59 ± 9	58 ± 6
Coated (mm Hg)	62 ± 11	67 ± 27	54 ± 8	55 ± 12	59 ± 24	59 ± 10	54 ± 8
<i>p</i> value	0.79	0.53	0.09	0.69	0.80	0.94	0.31
LAP	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (mm Hg)	3.3 ± 2.5	3.5 ± 1.6	3.5 ± 2.3	3.7 ± 2.1	4.4 ± 3.3	4.4 ± 2.0	5.1 ± 1.2
Coated (mm Hg)	6.9 ± 2.2	6.2 ± 4.2	4.7 ± 2.7	4.8 ± 1.9	6.2 ± 2.8	5.6 ± 2.6	6.0 ± 3.0
<i>p</i> value	0.02	0.18	0.42	0.36	0.33	0.39	0.49
CVP	10 min	1 hr	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs
Noncoated (mm Hg)	1.9 ± 2.3	2.6 ± 2.4	2.9 ± 2.9	2.5 ± 2.1	2.7 ± 1.8	3.0 ± 1.7	3.3 ± 1.2
Coated (mm Hg)	3.8 ± 3.3	2.9 ± 2.4	2.9 ± 2.7	3.4 ± 2.2	3.5 ± 2.7	3.6 ± 2.8	4.5 ± 3.6
<i>p</i> value	0.28	0.82	0.99	0.47	0.57	0.65	0.46

CPB, cardiopulmonary bypass; mAP, mean arterial pressure; LAP, left atrial pressure; CVP, central venous pressure.