Circuits with surface modifying additive alter the haemodynamic response to cardiopulmonary bypass

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Abstract

Objective: Blood contact with synthetic surfaces during cardiopulmonary bypass (CPB), inevitably results in the activation of a variety of interrelated pathways of inflammation and coagulation that may contribute to postoperative complications in cardiac surgery patients. The objective of this trial was to evaluate clinical events and complement activation related to the use of a novel biomaterial, into which a surface modifying additive had been incorporated into the polymer used to prepare the bypass circuit. Methods: A prospective, double-blind trial was carried out with 34 patients randomized to surgery, with either a standard circuit or a circuit treated (‘tip to tip’) with the surface modifying additive. Variables recorded included perioperative haemodynamics, volume replacement, α-agonist and inotrope use. Terminal complement complex (SC5b-9) was measured using an ELISA. Results: Upon initiation of bypass, there was a decrease in mean arterial pressure (MAP) in the control group, not seen in the test group ($P = 0.0005$, ANOVA). There was a decrease in the total volume of replacement fluid given intraoperatively in the test group as compared with the control group (total plus prime; control 5.3 ± 1.2 L, test 4.4 ± 1.9 L, $P = 0.03$, Mann–Whitney test). There was a trend to decreased need for inotrope infusion in the test group after CPB (test 1/17, control 6/17, Fisher exact test; $P = 0.085$). No difference was seen in the generation of terminal complement complex between the groups either during or after CPB. Conclusions: The decrease in blood pressure in the control group, upon the initiation of CPB, did not occur in patients undergoing CPB with the circuit prepared with the surface modifying additive. The decrease in blood pressure was likely associated with the increase in total administered fluids intraoperatively (approximately 1 l/patient) and perhaps the trend towards higher use of inotropes in the control patients as opposed to the test patients. These haemodynamic changes did not appear to be related to complement activation early in CPB. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Cardiopulmonary bypass; Complement activation; Blood pressure response; Biocompatibility

1. Introduction

In recent years, a variety of new biomaterials have been introduced, endeavouring to minimize the systemic effects of blood contact with artificial surfaces such as during cardiopulmonary bypass (CPB). This is particularly important due to the compromised immune and autonomic regulatory systems of the predominantly elderly patients undergoing cardiac surgery. Even with these modifications, complex changes inevitably occur within milliseconds after blood contact with any non-endothelial surface, resulting in activation of a variety of inter-related pathways that may contribute to inflammation and coagulation despite adequate heparinization.

A novel biomaterial approach to limit systemic events has involved the addition of a polysiloxane-containing co-polymer to the base polymer resin during manufacture of the CPB circuit. The former co-polymer migrates to the surface during fabrication, creating regions of alternating hydrophilic and hydrophobic domains. In vitro and in vivo studies, there has been promising evidence that the detrimental effects of the blood-biomaterial interaction may be mini-

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mized [1,2]. We have recently completed a clinical trial to evaluate a variety of laboratory and clinical parameters involving this new biomaterial in CPB [3]. Haemotological biocompatibility was significantly improved with this modified surface as compared with control circuits. The objective of the current trial was to determine if the dramatic blood changes seen in these patients were paralleled by systemic changes in haemodynamics and complement activation, as determined by generation of the terminal complement complex SC5b-9.

2. Materials and methods

A total of 36 patients scheduled for elective primary coronary artery bypass operations necessitating CPB were recruited for this study. The institutional human research ethics committee approved the study protocol and informed consent was obtained from all patients. The patients were excluded if they had major systemic illnesses (e.g. insulin-dependent diabetes with organ failure, renal failure), preoperative platelet or coagulation abnormalities, anticipated haemodilution during CPB of <21%, or they were taking anticoagulant or antiplatelet medications. All patients were requested to stop taking their aspirin 7 days prior to their surgery.

The patients were randomly assigned to surgery with either the test circuit (COBE SMARTrTM Biocompatible Extracorporeal Circuit, COBE Cardiovascular, Arvada, CO) or a standard untreated circuit. The perfusionist assigned the treatment immediately preoperatively, by opening a sealed, numbered envelope prior to set-up of the extracorporeal circuit. The randomization was accomplished using a random number table [4]. The cannulae and tubing used in these two circuits were identical in appearance, so that all members of the surgical and anaesthesia teams, excluding the perfusionist, were blinded to the patient designation.

2.1. Anaesthetic management

All cardiac medications excluding aspirin, were continued up to the day of surgery. The premedication included diazepam and morphine. The patients were monitored with a radial arterial pressure line and a Swan–Ganz catheter, inserted prior to intubation. The anaesthetic induction included midazolam 0.04 mg/kg, sufentanil 0.5 µg/kg, rocuronium 1 mg/kg and ketamine 1.5 mg/kg. Anaesthetic was maintained with midazolam 0.5 µg/kg per min, sufentanil 0.5 µg/kg per h, rocuronium 10 µg/kg per min and isoflurane as required to maintain haemodynamic stability.

2.2. Conduct of CPB

Prior to bypass, all patients were anticoagulated with porcine heparin (Organon Teknika, Toronto, Canada) to achieve a kaolin driven ACT > 480 s. Initial dosing was prescribed by a heparin dose response with Hepcon instrumentation (Hemotec, Medtronic, Parker, CO). Heparin (4500 units) was also added to the 1.5 l pump prime to establish a 3.0 units ml⁻¹ concentration. Upon initiation of bypass, the heparin serum concentration was monitored every 20 min by way of Hepcon automated protamine assay and subsequent doses of heparin were administered as needed to sustain a heparin level of 3.0 units ml⁻¹ [5]. Following the termination of CPB, heparin reversal was accomplished with a 1.1 protamine/heparin ratio (mg/mg) dose of protamine sulphate (Fujisawa Canada, Ontario, Canada) based on the final heparin serum concentration assayed.

CPB was conducted using a roller pump, a flat sheet polypolyethylene 1.3 m² membrane oxygenator (COBE CML DuoTrTM, COBE Cardiovascular Arvada, CO), a 43 µ arterial filter (COBE SentryTM), a closed venous reservoir bag, ascending aortic cannula, and a two-stage single venous cannula return. As noted above, all of the surfaces in the test group, including the cannulae and the filters, were prepared with the surface modifying additive co-polymer. Bypass flows were maintained at 2.4–3.2 l/m² per min. The body temperature was initially reduced to a systemic temperature of 32°C.

Hypotensive episodes, where the mean arterial pressure (MAP) was less than 50 mmHg were treated with 100 µ boluses of phenylephrine until the MAP exceeded 55 mmHg, and blood flows were raised but not to exceed 3.2 l/min per m². Hypertensive episodes, where the MAP exceeded > 90 mmHg, were treated with Isoflurane vapour (0.5–2.0% of membrane ventilation gas). In addition, minute blood flows were sustained to obtain a minimum venous haemoglobin saturation of 65 and 75% at nasopharyngeal temperatures of 36 and 32°C, respectively. Fluids (Ringers Lactate, pentastarch) were given by the perfusionist as needed to treat hypotension and low filling pressures. Fluids were also given by the anaesthetist after CPB as necessary, to maintain preload up to a pulmonary capillary wedge pressure of 18 mmHg.

Cardiac arrest was achieved using topical pericardial saline irrigation as well as antegrade cold crystalloid cardioplegia via the aortic root or the bypass grafts, at 20-min intervals. As there was no cardiostomy reservoir (integrated or otherwise), cardiac venting was accomplished via the aortic root by gravity drainage directly into the venous CPB line. All CPB solutions were filtered by a 40 µm transfusion filter (SQ40S Pall Biomedical Products, NY). At the completion of the procedure, the patient was rewarmed to a nasopharyngeal temperature of 37°C and then weaned from CPB after mechanical ventilation had been re-commenced. All scavenged blood from the mediastinum, collected intraoperatively and up to 4 h post-operatively, was processed by filtration (30 µm), centrifugation and washing (BRATTM, COBE Cardiovascular) prior to re-infusion.
2.3. Collection of blood specimens and measurement of plasma haemoglobin and terminal complement complex

Blood specimens were obtained from the side-port of the central line cords after removal of six dead space volumes of blood. The sampling was carried out at the following time points.

1. Insertion of the central line.
2. Five minutes after heparin administration.
3. Ten, 20, 40 and 60 min on CPB.
4. Ten minutes after administration of protamine.
5. Twenty-four hours after the administration of protamine.

Blood samples were taken into citrate (3.8%) on ice, then centrifuged to produce platelet poor plasma (PPP).

Routine haematology parameters were then determined including the WBC count (Serono, Model 9000, Baker Diagnostic, Allentown, PA). The Quidel SC5b-9 Enzyme Immunoassay (Quidel, San Diego, CA) was used for the quantitation of the terminal complement complex SC5b-9 in samples of blood.

2.4. Management of inotropic agents and fluids after CPB

The anaesthesia staff, during withdrawal from CPB, administered ephedrine hydrochloride or calcium chloride, in the presence of hypotension, if the cardiac contraction, as determined by transthoracic echo or direct inspection was adequate. Intravenous inotrope infusions were administered to patients separating from CPB if the cardiac index was <2.2 l/min per m² in the presence of an adequate preload. The choice of inotrope (dopamine, dobutamine, noradrenaline or milrinone) was left to the discretion of the anaesthetist. Post-CPB, all patients were given an infusion of 500 ml of Ringers Lactate or pentastarch (Ringers Lactate or pentastarch) were administered by the intensivist for hypovolemia (PCWP (Ringers Lactate or pentastarch) were administered by the intensivist for hypovolemia (PCWP < 12 mmHg) in the presence of decreased CI, low urine output (<0.5 ml/kg per h) or hypotension.

2.5. Data analysis and statistics

Continuous variables were analyzed using unpaired t-tests and categorical variables were analyzed using a chi-squared test or Fisher’s exact test as appropriate. Repeated measures were analyzed using repeated measures ANOVA. If the ANOVA was significant (P < 0.05), then unpaired t-tests were done at individual time points using the Bonferroni correction for multiple testing. Data that was not normally distributed were analyzed using the Mann–Whitney tests.

3. Results

Thirty-six adult patients scheduled for cardiac surgery requiring CPB were enrolled in this study during a 12-month interval. There were no differences in demographic or operative variables between the two cohorts, although there was a trend towards an increased number of class III ventricles in the control group (P = 0.06) (Table 1). There were two exclusions from the study (both in the control group). In the first case, there were technical problems with a gastroepiploic graft which necessitated urgent revision on bypass with a regular oxygenator. In the second case, the venting through the standard aortic root angiocatheter was inadequate, and the aortic root was opened directly for aspiration. This resulted in a significant air-blood interface which may have obscured the haematologic changes. In neither case, were the complications related to the type of bypass circuit utilized. Neither case was associated with mortality, although one patient did require an intraaortic balloon pump postoperatively. Amongst the patients who remained in the study, there was no mortality, there were no cases of perioperative myocardial infarction and no patients required an intraaortic balloon pump. One patient in the control group suffered a stroke in the territory of the right posterior cerebral artery.

Amongst the remaining 34 patients, there was complete follow-up throughout the study. The estimated intraoperative blood loss was not different between the two groups (control, 1.48 ± 0.39 l; test, 1.32 ± 0.38 l). Only one patient (control) required re-exploration for excessive bleeding after surgery. No surgical site was identified in this patient and there was no evidence of coagulopathy (normal INR, aPTT, platelet count and fibrinogen). After the re-exploration, the bleeding ceased and the patient did not receive any blood products. There was no difference demonstrated in the amount of blood collected from the mediastinum after the administration of protamine, up to the removal of the chest tubes (Table 2). There was also no difference in the

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 17)</th>
<th>Test (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year ± SD)</td>
<td>55.7 ± 7.4</td>
<td>60.2 ± 9.4</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>0</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Weight (kg ± SD)</td>
<td>86.8 ± 9.8</td>
<td>86.0 ± 16.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (35.3)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (23.5)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>12 (70.6)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>Ventricular class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (23.5)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>I</td>
<td>5 (29.4)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>II</td>
<td>2 (11.8)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>III</td>
<td>5 (29.4)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>Left main disease</td>
<td>3 (17.6)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Number of grafts</td>
<td>3.24 ± 0.66</td>
<td>3.41 ± 0.94</td>
</tr>
<tr>
<td>Total CPB time (min ± SD)</td>
<td>84.5 ± 16.9</td>
<td>88.4 ± 24.7</td>
</tr>
<tr>
<td>Cross-clamp time (min ± SD)</td>
<td>49.9 ± 11.2</td>
<td>53.5 ± 21.6</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate percentages. No significant differences were found between the groups. SD, standard deviation.
amount of postoperative washed blood that was re-administered (control, 359 ± 192 ml; test, 280 ± 299 ml, P = 0.3694).

One patient in the control group and one patient in the test group required 1 unit of autologous blood, whereas one patient in the test group received 2 units of autologous blood. One patient (test group) required the transfusion of 2 units of FFP. In this case, there was excessive bleeding accompanied by a prolonged INR (>1.7). Cryoprecipitate was also given to this patient.

Upon initiation of CPB, there was notable decrease in the MAP in the control group, not seen in the test group (Fig. 1, P = 0.0005, ANOVA). Within 5 min of the initiation of CPB however, the pressure increased to match the pressure in the test group, and no further differences in pressure occurred. There was a trend to a decrease in the total administered neosynephrine but this was not significant (test group median 0 mg, interquartile range 1200 mg, control group median 300 mg, interquartile range 1100 mg, P = 0.231, Mann–Whitney test). There was a significant decrease in the total volume of replacement fluid given intraoperatively in the test group as compared to the control group (Fig. 2, total plus prime; control 5.3 ± 1.2 l, test 4.4 ± 1.9 l, P = 0.03, Mann–Whitney test). There was no difference in fluid administration in the first 24 h postoperatively.

Some of the patients required a single dose of ephedrine hydrochloride or calcium chloride, when separating from bypass to augment the systemic vascular resistance. Amongst this group, there were seven patients in the control group and 12 patients in the test group. In none of these cases, were subsequent inotropes required. There was no difference in cardiac index and left ventricular stroke work index in the two groups (Table 3). There was a trend to decreased need for inotrope infusion in the test group after CPB (test 1/17, control 6/17, Fisher exact test; P = 0.085). Inotropes were required as infusions in six of the control patients (four dopamine, two noradrenaline) and one of the test patients (dobutamine). However, in the control group, in which there were more class III ventricles preoperatively, three of the patients requiring inotropes had this degree of ventricular dysfunction. The single patient requiring inotropes in the test group had a class II ventricle.

Terminal complement complex (SC5b-9), which has recently been demonstrated to be a sensitive marker of complement activation, was identical in both groups, throughout CPB (Fig. 3). There was no statistically significant difference in WBC count in the two groups, both during and after CPB (results not shown).

Table 2
Post-CPB blood loss

<table>
<thead>
<tr>
<th></th>
<th>Control (ml ± SD)</th>
<th>Test (ml ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-protamine - chest closure</td>
<td>347 ± 198</td>
<td>316 ± 139</td>
</tr>
<tr>
<td>0-6 h (ICU)</td>
<td>626 ± 309</td>
<td>511 ± 219</td>
</tr>
<tr>
<td>6-24 h (ICU)</td>
<td>532 ± 159</td>
<td>572 ± 260</td>
</tr>
<tr>
<td>24 h-removal (ICU)</td>
<td>76 ± 117</td>
<td>120 ± 197</td>
</tr>
<tr>
<td>Total drainage</td>
<td>1581 ± 450</td>
<td>1551 ± 642</td>
</tr>
</tbody>
</table>

No significant differences were found between the groups. SD, standard deviation.

Table 3
Pre- and postoperative haemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Test</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(l min⁻¹ m⁻² ± SD)</td>
<td>Post-bypass</td>
<td>2.44 ± 0.51</td>
</tr>
<tr>
<td></td>
<td>Pre-bypass</td>
<td>2.61 ± 0.56</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g m⁻¹ beat⁻¹ m⁻² ± SD)</td>
<td>Pre-bypass</td>
<td>40.8 ± 10.5</td>
</tr>
<tr>
<td></td>
<td>Post-prolamine</td>
<td>2.36 ± 0.51</td>
</tr>
</tbody>
</table>

No significant differences were found between the groups. SD, standard deviation.
enough to require an intervention in most cases. This hypo-
decrease in blood pressure in the control patients was large
the test and control groups upon the initiation of CPB. The
difference was identified in the blood pressure response of
patients were evaluated in the current study. Here, a marked
thrombin generation and decreased release of tissue plas-
significant decrease in platelet activation as reflected by
cardiac surgery [3]. The changes identified included a
be related to postoperative bleeding, thromboembolic
demonstrated that this modification results in significantly
a stable microdomain-like configuration. We have recently
caprolactone-polydimethylsiloxane-polycaprolactone [6,7].
The additive is a triblock-copolymer
were not specifically identified on scanning electron
immediate and significant consequence of the blood-bioma-
activation of complement. To support this, it has been pre-
ly responsible for the significant increase in
the total administered fluids (approximately 1 l per patient).
It was also likely related to a trend towards a greater mean
dose of neosynephrine during CPB and a trend to the more
frequent use of inotropic infusions after CPB in the control
patients. The immediacy of the hypotensive response suggests that
a soluble agent is released in the control group, mediating
vascular. Arvada, CO) [6]. The additive was incorporated into the polymer
used to prepare the circuit (SMARX \textsuperscript{T}M , COBE, Cardiovas-
culation of CPB to a novel biomaterial, into which a surface
modifying additive had been incorporated into the polymer
parallel the rapid hypotensive response seen in our trial.
was definitely a marked increase in debris on the
micrographs in the arterial filters collected from this trial [3]
yet, there was definitely a marked increase in debris on the
control surfaces which may have consisted of cellular ele-
the nature of this debris will need to be clarified in future
studies. In a similar clinical trial assessing circuits
preparation with surface modifying additives, Gu et al. [11] did
not show any difference in total elastase release between
patients undergoing bypass with this test surface, and a
control surface. In both groups, elastase did increase, how-
ever, the changes were not immediate and did not seem to
parallel the rapid hypotensive response seen in our trial.
There are many other products that may be released from
activated PMNs which should be re-assessed in further
trials. Moreover, the time course of their release and any
relationship to platelet-neutrophil aggregate formation
should be evaluated [12,13].
Finally, we have considered that the immediate decrease
in blood pressure may be related to endothelial-derived
relaxing factor (EDRF) release from endothelial cells, trig-
ger by the onset of CPB. This endothelial product is pre-
Fig. 3. Terminal complement complex (SC5b-9) (mean ± SEM) measured using an ELISA from blood samples taken at the time intervals indicated in
Section 2.

4. Discussion

The degree of biocompatibility of a biomaterial utilized in the fabrication of a CPB circuit may be reflected by the systemic manifestations in the patient both during and after the pump run. In extreme cases, bioincompatibility may contribute to some of the detrimental complications seen after cardiac surgery, such as cardiac and pulmonary dysfunction. The mechanisms by which these changes are produced are varied but are often closely inter-related. The experiments reported in this trial evaluated the haemodynamic clinical consequences of blood exposure during routine CPB to a novel biomaterial, into which a surface modifying additive had been incorporated into the polymer which may be related to postoperative bleeding, thromboembolic complications and homologous blood product usage after cardiac surgery [3]. The changes identified included a significant decrease in platelet activation as reflected by de-creased expression of platelet GMP-140, decreased thrombin generation and decreased release of tissue plasminogen activator [3]. There was also a marked preservation of the platelet count both during and after bypass [3].
The systemic and clinical changes in this same group of patients were evaluated in the current study. Here, a marked difference was identified in the blood pressure response of the test and control groups upon the initiation of CPB. The decrease in blood pressure in the control patients was large enough to require an intervention in most cases. This hypo-
sent within immediately-available intracellular stores [14] and is well-known to be the most potent vasodilator in vivo. However, because of its extremely short half-life, it is difficult to identify its presence as a causative agent and levels have not been measured during the course of bypass. Alternatively, but less likely, exposure of blood to the test surface results in release of the counterpart vasoconstrictive agent endothelin-1. However, there are virtually no intracellular stores of this agent, and its production is regulated at the transcriptional level, suggesting a time response for its release that would correlate poorly with the blood pressure changes seen in the present trial [15].

In conclusion, the use of a surface modifying additive prevented the initial hypotension related to the initiation of CPB, in patients undergoing elective coronary artery bypass grafting. The hypotension correlated with increased intraoperative fluid requirements in these patients. The causative mechanism for the protective influence of the test circuit was not related to complement activation. Further trials will be necessary to clarify the inter-relationship of PMN activation and platelet preservation during CPB with this surface, and to evaluate the role of EDRF release in the early stages of CPB in this phenomenon.

Acknowledgements

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References