Heparin Coated Cardiopulmonary Bypass Circuits in Coronary Artery Surgery - A Clinical Study

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Keywords: Blood coagulation, blood platelets, cardiopulmonary bypass, extracorporeal circulation, heparin.

Abstract

Cardiopulmonary bypass with systemic heparinization causes trauma to blood cells and coagulation defects. Artificial surfaces could be coated by end-linkage binding of heparin (Carmeda Bioactive Surface CBAS™). The use of such surfaces during cardiopulmonary bypass in animals resulted in less postoperative blood loss and better preservation of blood cells. Heparin-coated circuits were employed during coronary artery grafting in seven patients (Group C). Concomitantly, the heparin dose was reduced by 25% and an ACT of 300 sec was accepted. An additional seven patients were operated with non-coated circuits (Group NC), requiring an ACT above 400 sec with normal doses of heparin. There was no thrombo-embolic complications in Group C. The postoperative bleeding was generally low and without significant intergroup differences. Coagulation parameters displayed a significantly lower ACT and anti-Factor Xa during bypass in Group 1C. A tendency towards less blood cell trauma was observed with heparin-coated circuits, although the differences did not reach statistical significance. The protamine dose could be reduced by 50%, which significantly reduced the protamine/heparin quotient.

This study indicates that routine cardiopulmonary bypass could safely be performed with heparin-coated circuits and reduced intravenous doses of heparin and protamine. It is suggested that the use of heparin-coated circuits may lead to less blood cell trauma.

Introduction

Cardiopulmonary bypass (CPB) has various effects on biologic cascade systems including hemostatic disturbances (1,2). Damaging effects on leucocytes, red blood cells and activation of the complement system are well documented (3,4,5) and may lead to organ damage and dysfunction (6,7). The negative effects of CPB are partly related to high doses of heparin and protamine as well as lack of biocompatibility of the CPB circuit itself.

Much effort has been spent to find techniques for coating artificial surfaces with biologically active heparin. CPB circuits with such a surface would permit lower doses of heparin and protamine and might also be more biocompatible. The Carmeda Bioactive Surface (CBASTM, Carmeda, Sweden) is coated by end-linkage binding of heparin molecules to the artificial surface (8). This method binds heparin stable and without loss of biological activity. The surface inhibits thrombin activation and is also platelet compatible (9,10,11). It has been demonstrated in animal studies that heparin-coated CPB circuits reduce the need for systemic heparinization and protamine, thereby reducing postoperative bleeding (12). Platelets, leucocytes and erythrocytes were also better preserved and there was less activation of the complement system (12, 13). In vitro studies with coated surfaces have shown reduced granulocyte activation (14).

In this study, we have used heparin coated CPB circuits and concomitantly reduced heparin doses by 25% during coronary artery bypass surgery. Non-coated systems and normal doses of heparin were used in the controls.

Material and Methods

The study included 14 patients, (NYHA III) with two or three vessel disease, scheduled for elective coronary artery bypass grafting. All patients had normal coagulation parameters. Patients with diabetes, neurologic disease, renal insufficiency or on anticoagulation therapy were not considered. All patients were operated with the use of left internal mammary artery and vein grafts.

Seven patients (Group C) were operated with the use of heparin-coated CPB circuits. These patients were given heparin in a reduced dose (225 IU/kg) and CPB was started when the activated clotting time (ACT) was above 300 sec. Additional heparin was given if the ACT was below 300 sec. The control group also included 7 patients (Group NC), who were operated with non-coated devices. They received a normal dose of heparin (300 IU/kg) and CPB was started when the ACT was above 400 sec. Additional heparin was given if the ACT was below 400 sec.

The study protocol conformed to the rules of the Helsinki declaration and was approved by the Ethics committee of the University of Uppsala. Informed consent was obtained from patients participating in the study.
Anesthesia

All patients were premedicated with morphine 0.125 mg/kg and scopolamine 0.005 mg/kg one hour before they were taken to the operating theatre. Anesthesia was induced with fentanyl 5 
μg/kg and thiopental 2-4 mg/kg. Neuromuscular relaxation was obtained with pancuronium 0.1 mg/kg. The patients were ventilated with 50% nitrous oxide in oxygen until shortly before CPB, when nitrous oxide was discontinued. Anesthesia was maintained with additional doses of fentanyl and isoflurane. Nitroglycerin and additional pancuronium were given when necessary.

Cardiopulmonary bypass

A Stockert heart-lung machine (Germany) with a roller pump was used. The CPB circuit consisted of a membrane oxygenator (Maxima, Medtronic, USA) connected to a collapsible soft venous reservoir (Medtronic, USA) and an arterial filter (40 μm Intercept, Medtronic, USA). The CPB circuit was primed with 2000 ml of Ringer’s acetate. There was no venting of the left ventricle or cardiotomy suction. A cell saver was used for suction (Haemonetics, USA). After bypass the remaining blood in the circuit was processed in the cell saver and retransfused.

The pump flow was non-pulsatile and initially 2.2 l/m². After body cooling to 30°C in the nasopharynx, pump flow was reduced by 25%. St Thomas’ cardioplegic solution (Plegisol, Abbot, England) was employed.

Biochemical analyses

Activated coagulation time (ACT) was determined by the Hattersley technique (15) including a Hemochron Model 400 analyzer and coagulation test tubes (Celite activated, CA 510). Anti-factor Xa (aFXa), representing the heparin concentration in plasma, was assayed amidolytically (COATEST Heparin, Kabi Diagnostica, Sweden). Samples with levels >0.7 IU/ml were diluted with human normal plasma to a ratio of 1:10 and further analyzed. Platelet count, leucocyte count and hematocrit were quantified with an automatic cell counter. Platelet adhesion was determined by glass retention test (16) using Adeplat S columns and an Adeplat pump (Semmelweiss, Italy). Platelet adhesion was expressed as adhesive platelet count in percent of total platelet count, reference value >72 %. Hemolysis was arbitrarily determined by photometric absorbance at 405 nm (A₄₀₅) of 75 μl plasma/2.7 ml phosphate-buffered saline (pH 7.4). The platelet and leucocyte counts were individually corrected for hemodilution, based on hematocrit, and expressed in percent of the preoperative value. Samples for coagulation parameters were collected after anesthesia, after heparinization, at the start of CPB, after 45 minutes of CPB, at the end of CPB, 15, 60, 120, 180, 240 minutes after protamine reversal and 20 hours postoperatively.

Samples for CK-MB were taken preoperatively, four hours and 24 hours postoperatively. They were analyzed with respect to activity of CK-isoenzymes following ion exchange fractioning. Samples for creatinine were taken preoperatively and every second day postoperatively during a week. Serum creatinine was measured with a Jaffe kinetic method.

Arterial blood gases were measured at 37°C (ABL4; Radiometer, Denmark) and were not corrected for temperature.

Respiratory function

The alveolo-arterial oxygen pressure gradient, PO₂ (A-a), was measured on three occasions. Preoperatively, the patient breathed in a mask supplied with oxygen (FiO₂=40%) during at least 20 minutes. This procedure was repeated three hours after bypass, if the patient was extubated. If not, an FiO₂ of 40 % was delivered by the ventilator. The third measurement was made the following morning, when all patients had been extubated. Blood gases were measured and PO₂ (A-a) was calculated according to the alveolar gas equation (PO₂(A-a) = FiO₂ * (Patm-6.3)-(PCO₂ * 0.8¹ PO₂)) and with a respiratory quotient of 0.8.

Statistics

Values are given as mean±SEM. Statistical analysis of the data was performed by Student’s t-test using a data base (MEDLOG™,Information and Analysis Corporations, Calif. USA). P<0.05 (*) was considered significant.

Results

Hemostatic and blood cell variables

Hematocrit decreased to about 27% during CPB because of hemodilution, followed by a normalization after CPB. There were no significant intergroup differences. Group C received a reduced dose of heparin while Group NC received normal dose (Table 1). There were significantly lower peroperative levels of

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<th>TABLE 1: Heparin-protamine dosages, bleeding and transfused blood products. Values are mean ± SEM</th>
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<td><strong>Group</strong></td>
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<td>Heparin IU/kg bolus</td>
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<td>Intrap. bloodloss ml</td>
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ACT (Figure la) and aFXa (Figure lb) in Group C. Consequently, Group C needed less protamine (Table 1) to achieve heparin reversal, as reflected by ACT and aFXa. The protamine-heparin ratio (Table 1) was reduced to 0.5 in two patients in Group C. Platelets decreased during CPB followed by postoperative restoration. However, correction for the
hemodilution revealed a relative increase in platelets of approximately 20% in both groups at the end of CPB and a drop of similar magnitude in Group NC after 20 hours (Figure 2a). Platelet adhesion (Figure 2b) was almost abolished at the start of CPB but returned towards normal levels one hour after protaminization, with no intergroup differences. Leucocytes increased during CPB and two hours after surgery, followed by a slow decrease (Figure 3). Hemolysis (Figure 4) was reduced during CPB and increased postoperatively without significant intergroup differences. Intra and postoperative bleeding displayed insignificant intergroup differences (Table 1).

**FIGURE 1:** A) Active Clotting Time (ACT) and b) Anti Factor Xa (aFXa) before, during and after CPB. Groups: C = coated and NC = not-coated Values are mean ± SEM. (* = p<0.05)

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**Biochemical variables**

Blood gases during CPB were within normal limits and without significant differences between the groups (Table 2). The alveolo-arterial oxygen pressure gradient, pO$_2$ (A-a), showed a slight increase after CPB in both groups (Table 2).

There were no significant differences in CK-MB 5 and 24 hours after CPB (Table 2). Both groups displayed a small increase in creatinine after CPB (Table 2).

**Clinical variables**

There were no signs of clotting in the CPB-line including the oxygenator, arterial filter and venous reservoir. No patients had focal neurological symptoms postoperatively.

There were no significant differences in CPB-time between group C and NC (87±7 vs. 101±7 min). No perioperative infarcts and postoperative mortality were noted. Two patients in Group C and three patients in Group NC needed inotropic support after CPB.

**Discussion**

Cardiopulmonary bypass is an unphysiologic environment for the organism. The blood is subjected to abnormal conditions regarding contact surfaces, temperature, anticoagulants and
anticoagulant reversal agents. Excessive bleeding following CPB is a reality and has multifactorial pathogenesis (17). The damage of blood components may also lead to organ dysfunction, sometimes recognized as "postperfusion syndrome". One possible way to diminish the risk of these complications would be to reduce the thrombogenicity and to improve the biocompatibility of the artificial surfaces by using heparin-coated extracorporeal circuits.

This is the first clinical study where CBAS™ coated systems have been used during routine heart surgery. The most important finding was that coated circuits could be used safely without any identified thrombo-embolic complications. There were no signs of pulmonary, myocardial or renal damage (Table 2) and no neurologic defect was observed on clinical examination. This indicates that perfusion with heparin-coated circuits during heart surgery could be performed without any major impairments in organ perfusion.

The CBAS™ has a coating factor of 2 μg/cm², rendering about 60 mg of active heparin in the circuit itself. Consequently, to compare the effects of a coated surface versus a non-coated, patients receiving a coated circuit were given less heparin intravenously. Thus, both groups were exposed to approximately the same amount of active heparin. AntiFactor Xa reflects the plasma concentration of heparin. Both aFXa and ACT levels verified the lower systemic dose of heparin which had been given to Group C. These results also indicates that there was no important leakage of heparin from the coated surface. Along with the decreased amount of intravenous heparin the following protamine could be reduced to 50%. It was our clinical impression that heparin reversal was quicker as well as more efficient in Group C, and this was further indicated by the somewhat shorter ACT levels of this group.

The coagulation parameters did not show any significant postoperative differences between the groups. However, the tendencies were similar to our earlier results from animal experiments (12). In these experiments less postoperative bleeding was found when the heparin dose had been reduced by 75%, but not with a full dose of heparin (with coated circuits). Postoperative bleeding in the present study was generally low
and without significant differences between the groups. A further reduction of intravenous heparin may result in reduced postoperative blood loss.

Platelet adhesion reflects the ability of platelets to adhere to foreign surfaces and to damaged endothelium, representing the first step of platelet activation. Both groups in this study displayed a more rapid recovery in platelet adhesion than seen previously and the same tendency towards rapid recovery was seen in number of platelets and hemolysis (2). This indicates that a circuit with a hollow fiber membrane oxygenator and a collapsible venous reservoir, in itself is less harmful than previous systems. The exclusion of cardiotomy suction may also have been beneficial to blood cell preservation. Such a device may trigger thrombus formation during periods of low or no blood flow and by mixing of air and blood. Vентing of the left ventricle was not applied since this could also trigger clotting, by periods of low or no flow in the venting line. We did not experience any technical difficulties in performing surgery under these circumstances.

In order to achieve normal blood gases during CPB both groups needed gas flow of the same level to the oxygenators. This indicates that the gas flux over the hollow fiber membranes is unaffected by the coating process.

The CBAS™ coating has been used clinically for long lasting perfusions (heart and lung assist) with varying doses of systemic heparinization (18, personal communication, Jennerberg, Carmeda). In the majority of such perfusions clotting has not been a problem as long as there has been a high pump flow.

In summary, standard CPB perfusions for coronary artery surgery were performed with a heparin coated circuit and a 25% reduction in systemic heparinization. There were no signs of clotting or embolic events. A tendency towards less blood cell trauma was observed together with heparin-coated circuits, although not verified statistically. This may partly be explained by the small number of patients involved in the study. A further reduction of the systemic heparin dose may result in even less postoperative bleeding and blood cell trauma. Controlled clinical trials are needed.

Acknowledgement

The technical assistance of Ms. Lena Larsson is greatly appreciated. The laboratory analyses were performed at the department of Forensic Medicine, Uppsala University and the department of Clinical Chemistry, University Hospital, Uppsala, Sweden. The study was supported by grants from the Swedish Heart Lung Foundation.

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