Heparin-coated circuit in coronary surgery
A clinical study

Abstract We performed a randomized study in 101 patients who underwent routine isolated coronary bypass graft surgery. In 50 cases an entire coated Carmeda circuit was used (coated group), and an uncoated circuit in the remaining 51 (uncoated group). A Medtronic Maxima oxygenator and a Biomedicus Biohead were used in all cases. Patients with coated circuits received low systemic heparinization with a heparin loading dose of 200 IU/kg, and 300 IU/kg for the control. Activated coagulation time was maintained at more than 275 s for the coated group versus more than 400 s for the uncoated one. The mean age of patients was 64.1±9.6 for coated and 63.5±9.7 for the uncoated group. The number of coronary grafts was 3.1±0.7 for the coated group and 3.1±0.1 for the uncoated group. Cross-clamp and bypass times were 53±14 and 98±24 min for the coated, versus 57±15 and 104±24 for the uncoated, group. Chest drainage was 989.4±509.5 ml for the coated group versus 1435±1027 for the uncoated one (P<0.02). The amount of transfused homologous blood was 723±597 ml for the coated group versus 1071±831 ml for the uncoated one (P<0.03). Postoperative endotracheal intubation time was 12.1±3.6 h for the coated and 14.6±4.5 h for the uncoated group (P<0.05). Bleeding required rethoracotomy in 1/50 of the coated group, and in 4/51 of the uncoated one. Hospital mortality was 1/50 in the coated, and 4/51 in the uncoated, group. In our preliminary experience, heparin coating of an extracorporeal circuit reduces postoperative blood loss and blood transfusions in routine coronary bypass operations. [Eur J Cardio-thorac Surg (1996) 10: 48–53]

Key words Heparin surface coating · Anticoagulation · Heparin · Extracorporeal circulation · Cardiopulmonary bypass

Introduction

Extracorporeal circulation requires systemic heparinization in order to prevent circuit thrombosis. Blood outside the human body is not compatible with the artificial materials of the extracorporeal circuit line. The foreign surface interaction initiates a host of biological reactions, involving whole defensive systems in the human body. During extracorporeal circulation (EC) of the blood, it is the exposure of blood to large areas of artificial materials that disrupts the normal state and activates these defensive systems. The latter involve blood elements such as activation and consumption of platelets, activation of leucocytes and destruction of red blood cells as well as many other interrelated reactions and substances such as destructive enzymes released from blood cells, anaphylactic reactions, endotoxins, etc. These biological reactions combined together affect the heart, lungs, kidneys, brain and other organs to cause conditions known as "postperfusion syndrome" or "whole body inflammatory response" [17].
Heparin surface coating was introduced by Gott in 1963 [11], and Larm [19] improved the stability of this complex through end-point attachment of heparin by covalent bonding. Improved heparin surface coating of tubings, cannu-
las, oxygenators, centrifugal pump heads, as well as con-
nectors became possible. Experimental and clinical stud-
ies have shown reductions of complement and neutrophil activation, administration of homologous blood products, and heparin-protamine requirements [12, 15, 25, 32, 33].
The present study was performed to compare, during routine coronary bypass operations, a heparin-coated card-
diopulmonary bypass (CPB) circuit to a standard uncoated circuit and to evaluate the possible benefits of moderately reduced systemic heparinization used with the coated circuit.

Material and methods
The study was conducted in 101 consecutive patients who underwent isolated coronary artery surgery at this Institution after informed consent from November, 1993 to March, 1994. The patients were randomly assigned for CPB with or without a coated EC. In the 51 pa-
tients with uncoated circuit (uncoated group) the EC included a Bi-
omedicus vortex pump mounted on a Jostra heart/lung machine, with a Maxima membrane oxygenator with rigid venous reservoir, and arterial line 40 µ filter, and polyvinylchloride tubing. In the 50 patients with the coated circuit (coated group), all parts of the cir-
cuit were heparin-coated including a Maxima membrane oxygena-
tor with collapsible soft venous reservoir, all connectors, left ventricular venting, and all arterial and venous cannu-
las. As no heparin-coated cardiomyotomy suction was available, perioperative bleeding in the coated group was collected and quantified in a standard cardiomyotomy reservoir and was only retransfused after the end of CPB if the amount of hemodiluted blood exceed 500 ml. The perioperative bleeding in the uncoated group was al-
ways retransfused.

After premedication of the patient with bromazepam (3-6 mg), anesthesia was induced with sufentanil (0.20-0.30 mg), mida-
zolam (0.1-0.3 mg/kg), atracurium (0.5 mg/kg), and etomidate (0.3 mg/kg). Ventilation was controlled with air and oxygen. Anal-
gesia was provided with midazolam and sufentanil. After a median sternotomy, a bolus of bovine heparin was administered (300 IU/kg body weight in the uncoated, and 200 IU/kg in the coated, group). Heparinization was checked by the activated clotting time (ACT) and, if necessary, additional heparin was administered to maintain an ACT at approximately 400s in the uncoated, and 275s in the coat-
ed, group. No steroids were given. The EC was primed with Plasma-
lyte and sodium bicarbonate, without heparin for the coated group versus 4000 IU/L for the uncoated group. Cardiopulmonary bypass was performed with cardioplegic arrest and moderate hypothermia (33°C nasopharyngeal temperature) with pump flows of 2.2 l/min per min, and the maintenance of mean arterial blood pressures of 50-60 mmHg. After CPB, heparin was neutralized by means of pro-
tamine chloride (3 mg/kg for the uncoated, and 2 mg/kg for the coat-
ed, group). Arterial blood was sampled after the induction of anes-
thesia, after heparinization, after 30 and 45 min on CPB, at prota-
mise infusion time, and 4.8 and 24 h postoperatively. Hematocrit and platelet counts, and levels of D-dimer and haptoglobin were de-
termined. Perioperative urinary production and diuretic administra-
tion were recorded. Perioperative and postoperative levels of serum creatinine and urea were determined. Total postoperative blood loss was recorded until the chest tubes were removed. Homologous red cells were transfused if hematocrit was less than 20% during CPB or less than 25% after surgery. For volume replacement, plasma and/or 20% albumin solution were also transfused.

In our study quantitative variables were tested for normal distri-
bution and compared using Student’s (two-tailed t-test). Differences in group proportions were assessed using χ² test or, for small numbers, using Fisher’s exact test. Results were expressed as the mean ± standard deviation of the mean, and a P' value of less than 0.05 was considered to be significant.

Results
The preoperative and intraoperative clinical data were simi-
lar in the two groups. The total heparin dose was signifi-
cantly lower in the coated, than in the uncoated, group. The protamine doses were correspondingly low as a result of the low dose of heparin (Table 1). Perioperative ACT values were lower in the coated, than in the uncoated, group (Fig. 1). The mean aortic occlusion time for all cases in the coated group was 53±14 min, and 57±15 min in the un-
coated one. The mean CPB time was 98.8±24.5 min for the coated, and 104.2±24.8 min for the uncoated group. In only two patients of the coated group was perioperative bleeding in the cardiotomy reservoir retransfused at the end of CPB.

The average blood loss via mediastinal drainage tubes was 989±509 ml in the coated, and 1435±1027 in the un-
coated group (P<0.02) at 24 h (Fig. 2). Bleeding was clearly less in the coated, than in the uncoated, group. The average transfusion requirement was only 723±597 ml of packed red blood cells for the coated (12 patients required no transfusions), and 1071±831 ml for the uncoated group (P<0.03) (Table 2). Only five patients of the uncoated group required no transfusions. The baseline preoperative hematocrit was slightly different, 42±3% for the coated group and 44±3% for the uncoated one and decreased at the end of CPB and on day 1 to 31.1±2.6% in the coated group versus 31.2±2.8 in the uncoated one (P<0.01) (Fig. 3). One patient in the coated, and four in the uncoated,
Fig. 1 Activated clotting time (ACT) before, during and after cardiopulmonary bypass (CPB)

Fig. 2 Total chest tube drainage versus total transfusion requirements. (Values in ml±SD)

Fig. 3 Hematocrit before, during and after cardiopulmonary bypass (CPB)

Fig. 4 D-dimers levels before, during and after cardiopulmonary bypass (CPB)

Table 2 Postoperative bleeding and transfusion profiles (means±SD)

<table>
<thead>
<tr>
<th></th>
<th>Carmeda</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding (ml)</td>
<td>989±509</td>
<td>1435±1027</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Transfusion (ml):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed red cells</td>
<td>723±597</td>
<td>1071±831</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Plasma</td>
<td>37±144</td>
<td>138±258</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Albumin</td>
<td>122±71</td>
<td>155±83</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group (2% versus 8%) were reoperated because of postoperative mediastinal bleeding. The preoperative platelet counts were 210.2±62.6×10⁹/µl for the coated group vs 216.2±39.2×10⁹/µl for the uncoated, one, and were similar at the end of CPB and in the postoperative period, 140.3±25.6 versus 139.1±39.1. Fibrinolysis was elevated in both groups during CPB. Preoperative levels of D-dimer were 1±0.8 mcg/ml for the coated group, and 0.55±0.23 for the uncoated one. At the end of bypass, values were 1.7±0.70 for the coated versus 1.50±0.78 mcg/ml for the uncoated group, the increase being more pronounced (P<0.05) in the uncoated group (Fig. 4). Preoperative haptoglobin blood levels were similar in the two groups 2.48±0.85 vs 2.21±1.09 g/l for the coated and uncoated groups, respectively. In the early postoperative period, there was a significantly more pronounced decrease of these values in the uncoated group (0.30±0.36 g/l) vs 0.76±0.45 g/l (P<0.0002) for the coated one (Fig. 5).

Urinary output during the operation was higher in the coated, (505.3±253.9 ml) than in the uncoated group (357.2±230.1 ml) (Table 3). Rises of serum creatinine and urea levels were lower in the coated than in the uncoated group during CPB. Diuretic doses were similar in the two groups. The mean time of endotracheal intubation was...
The contact between blood and the non-biological components of an EC results in significant abnormalities of hemostasis including platelet degranulation, prolonged bleeding time, reduction in the level of coagulation factors, complement activation and increased fibrinolytic activity [1, 2, 6, 7]. Heparin has been essential for anticoagulation during CPB since the beginning of the latter’s use. It has a rapid onset, effectively prevents clot formation and is rapidly and completely neutralized by protamine. Heparin and protamine possess some important limitations. Heparin activates and degranulates platelets, which may contribute to the platelet functional deficit that follows CPB. Systemic administration of heparin incompletely presents the adherence of fibrinogen and platelets to synthetic surfaces, and blood coagulation remains moderately active during CPB despite profound anticoagulation with heparin. Protamine is known to have complement-activating properties, causes vasodilatation and can cause life-threatening anaphylaxis or pulmonary hypertension. The optimal protamine dosage remains controversial, because inadequate doses fail to neutralize heparin-induced anticoagulation while excessive doses probably exacerbate coagulopathy after CPB and may contribute to adverse hemodynamic side effects. An activated clotting time of 450 s and greater has been recommended to improve thrombo-resistance [16, 19, 24].

Standard CPB circuits have poor biocompatibility and thrombo-resistance [28]. Despite research in the area of blood compatible materials, the most compatible surface remains the endothelial lining. Surfaces incorporating biologically active substances appear to be a more viable approach to blood-compatible surfaces. To avoid the disadvantages of systemic heparinization during CPB, especially during long-term application, many attempts have been made to find alternative solutions [3, 18, 23]. Coating of ECs with heparin may, at least theoretically, allow a reduction in systemic heparinization [5, 10, 21, 31–33] and also a reduction in protamine reversal dosage. Secondly, it may make ECs in general more biocompatible [4, 8, 13, 14, 20, 30].

The first successful attempt at binding heparin to prosthetic devices by ionic linking was reported by Gott [11]. Larm [19] improved the method, and his technique was used to produce the Carmeda Bio-Active surface. Experimental [22, 26, 27] and clinical [6, 7, 19] studies using heparin-coated circuits showed a reduction of complement activation, platelet adhesion, fibrin deposition and neutrophil degranulation. Bleeding is one of the most common complications after open-heart surgery and contributes to morbidity and early postoperative mortality [34]. One advantageous feature of a heparin-coated CPB system is the possibility of reducing the heparin dose. Von Segesser et al. (30–33) tested heparin-coated circuits with systemic anti-coagulation levels below those conventionally used for CPB in humans, and their results appear promising with respect to reducing the post-CPB blood loss.

In the present study, heparin and protamine doses in the coated group were 59% and 61% of the doses given to the uncoated group (P<0.05).

Two patients in each group had an uncomplicated perioperative myocardial infarction (MI). One patient in the uncoated group had a cerebrovascular event. One patient (2%) in the coated group (extensive MI) and four (8%) in the uncoated group (1 MI, 2 mesenteric ischemia, and 1 respiratory infection) died in hospital. The mean hospital stay was 12.4±3.2 days for the coated vs 16.2±4.4 days for the uncoated group (P<0.03).

Discussion

The contact between blood and the non-biological components of an EC results in significant abnormalities of hemostasis including platelet degranulation, prolonged bleeding time, reduction in the level of coagulation factors, complement activation and increased fibrinolytic activity [1, 2, 6, 7]. Heparin has been essential for anticoagulation during CPB since the beginning of the latter’s use. It has a rapid onset, effectively prevents clot formation and is rapidly and completely neutralized by protamine. Heparin and protamine possess some important limitations. Heparin activates and degranulates platelets, which may contribute to the platelet functional deficit that follows CPB. Systemic administration of heparin incompletely presents the adherence of fibrinogen and platelets to synthetic surfaces, and blood coagulation remains moderately active during CPB despite profound anticoagulation with heparin. Protamine is known to have complement-activating properties, causes vasodilatation and can cause life-threatening anaphylaxis or pulmonary hypertension. The optimal protamine dosage remains controversial, because inadequate doses fail to neutralize heparin-induced anticoagulation while excessive doses probably exacerbate coagulopathy after CPB and may contribute to adverse hemodynamic side effects. An activated clotting time of 450 s and greater has been recommended to improve thrombo-resistance [16, 19, 24].

Standard CPB circuits have poor biocompatibility and thrombo-resistance [28]. Despite research in the area of blood compatible materials, the most compatible surface remains the endothelial lining. Surfaces incorporating biologically active substances appear to be a more viable approach to blood-compatible surfaces. To avoid the disadvantages of systemic heparinization during CPB, especially during long-term application, many attempts have been made to find alternative solutions [3, 18, 23]. Coating of ECs with heparin may, at least theoretically, allow a reduction in systemic heparinization [5, 10, 21, 31–33] and also a reduction in protamine reversal dosage. Secondly, it may make ECs in general more biocompatible [4, 8, 13, 14, 20, 30].

The first successful attempt at binding heparin to prosthetic devices by ionic linking was reported by Gott [11]. Larm [19] improved the method, and his technique was used to produce the Carmeda Bio-Active surface. Experimental [22, 26, 27] and clinical [6, 7, 19] studies using heparin-coated circuits showed a reduction of complement activation, platelet adhesion, fibrin deposition and neutrophil degranulation. Bleeding is one of the most common complications after open-heart surgery and contributes to morbidity and early postoperative mortality [34]. One advantageous feature of a heparin-coated CPB system is the possibility of reducing the heparin dose. Von Segesser et al. (30–33) tested heparin-coated circuits with systemic anti-coagulation levels below those conventionally used for CPB in humans, and their results appear promising with respect to reducing the post-CPB blood loss.

In the present study, heparin and protamine doses in the coated group were 59% and 61% of the doses given to the uncoated group, thereby reducing the side effects directly and indirectly caused by heparin, protamine and heparin-protamine complexes. The mean hematocrit could be maintained at the same level in the group receiving low systemic heparinization as in the full heparinization group, despite the fact that the transfusion requirements in the former were significantly less than those in the latter. This is mainly due to the significant reduction in postoperative bleeding, in relation to the low dose of heparin and protamine administered to the coated group. It is important to mention the possible effects on bleeding due to the introduction of cardiotomy suction blood into the systemic cir-
culation of uncoated patients, which is known to incorporate many blood-activating products and to cause greater hemolysis and platelet inactivation [4]. The action of heparin on hemostasis involves platelets and fibrinolysis [9]. We found no statistically significant difference in platelet counts at the end of CPB. Fibrinogen degradation products, however, showed higher values in the uncoated group during CPB and the postoperative period. Also, CPB induces mechanical trauma to red cells, leading to hemolysis. During CPB hemolysis was significantly less in the coated group than in the uncoated one, as demonstrated by the more pronounced decrease of haptoglobin blood levels in the latter group. The greater urine output in the coated group may indicate less CPB organ damage related to reduced inflammatory response in this group.

The successful use of this circuit was accomplished in coronary patients, who benefited from the low-dose heparin and protamine requirements. Patients in the coated group had fewer intraoperative and postoperative complications. The mean time of tracheal intubation, serum creatinine and urea levels, and hospital stay were lower in the coated group. The biocompatibility characteristics of this circuit permit lower heparin requirements during CPB, which lead to decreased intraoperative and postoperative blood loss and reduction of transfusion-associated complications.

At the time of this study, the coated circuit is significantly more expensive than routine CPB equipment. The benefit in the application of this technology and the possible future reduction of cost may recommend the use of the coated circuit in all patients undergoing routine CPB. It will also be useful in patients who will benefit from reduced hepatrinization such as those undergoing aortic surgery, or in cases in which systemic hepatrinization is contraindicated such as for surgery in multiple trauma patients. Further clinical studies are needed to confirm these results.

Acknowledgements We are indebted to Mrs. Ana Aguirre, Maialen Aguirre, Karmele Perez, Teresa Rodriguez, Rosa Irigo and Itzyar Villar for the excellent technical assistance. Also to Drs. Angulo and Lobato for clinical chemical investigations.

References


