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Clinical evaluation of Duraflo® II heparin treated extracorporeal circulation circuits (2nd version)
The European working group on heparin coated extracorporeal circulation circuits

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Abstract

Objectives: To evaluate whether the application of heparin treated circuits for elective coronary artery surgery improves postoperative recovery, a European multicenter randomised clinical trial was carried out. Methods: In 11 European heart centers, 805 low-risk patients underwent cardiopulmonary bypass (CPB) with either an untreated circuit (n = 407) or an identical but heparin treated circuit (n = 398, Duraflo® II). Results: Significant differences were found among participating centers with respect to patient characteristics, blood handling procedures and postoperative care. The use of heparin treated circuits revealed no overall changes in blood loss, blood use, time on ventilator, occurrence of adverse events, morbidity, mortality, and intensive care stay. These results did not change after adjustment for centers and (other) prognostic factors as analysed with logistic regression. In both groups no clinical or technical (patient or device related) side effects were reported. Because female gender and aortic

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cross clamp time appeared as prognostic factors in the logistic regression analysis, a subgroup analysis with these variables was performed. In a subgroup of females \( n = 99 \), those receiving heparin treated circuits needed less blood products, had a lower incidence of rhythm disturbances and were extubated earlier than controls. In another subgroup of patients with aortic cross clamp time exceeding 60 min \( n = 197 \), the amount of patients requiring prolonged intensive care treatment \( (> 24 \text{ h}) \) was significantly lower when they received heparin treated circuits versus controls. **Conclusion:** These findings suggest that improved recovery can be expected with heparin treated circuits in specific higher risk patient populations (e.g. females) and when prolonged aortic cross clamp time is anticipated. Further investigations are recommended to analyse the clinical benefit of heparin treated circuits in studies with patients in different well defined risk categories and under better standardised circumstances. © 1997 Elsevier Science B.V.

**Keywords:** Cardiac surgery; Heparin treated extracorporeal circulation circuits; Clinical outcome; Multicenter clinical evaluation

1. Introduction

Blood in contact with artificial surfaces will clot. The introduction of systemic heparinisation prevents this clotting and has initiated the era of extracorporeal circulation. From the earliest sixties heparin treatment of blood contacting surfaces was attempted, for instance in order to eliminate or reduce systemic heparinisation and thereby improving postoperative haemostasis. However, it lasted about 30 years before an economic method became available to treat the surface of a whole extracorporeal circuit for cardiopulmonary bypass (CPB) \[14,25\]. In this particular situation, systemic heparinisation can indeed be reduced \[21,22\] though this is still controversial. In the situation of cardiac surgery the CPB circuit is not a ‘closed’ circuit in which blood only contacts the heparin treated surfaces. There remains blood-air and particularly blood-tissue contact (pericardial cavity) and as long as this occurs the clotting cascade is still intensively activated and systemic heparinisation has to be maintained at appropriate levels to prevent clotting during the CPB procedure \[23\].

Biochemical evaluation of the effect of heparin treated circuits on the activation of the plasmatic systems revealed that next to binding of circulating antithrombin III to the heparin treated surface inhibiting thrombin generation \[9\], also complement activation and granulocyte activation appears to be reduced \[4,7,15,16,24\]. Complement activation during CPB is considered to play a major role in the whole body inflammatory response after cardiac surgery and thereby contributes to postoperative morbidity and mortality \[5,13,20,27\]. The reduction of complement activation by heparin treatment may have even greater advantages than the decrease in bleeding originally expected. Despite significant reduction of complement activation with the use of heparin treated circuits, so far, no clear evidence of postoperative clinical improvements has been demonstrated \[7,8,18\]. Since all these biochemical studies were done in small patient groups, a multicenter trial with a large number of patients may reveal evidence in this regard.

To study clinical outcome in patients treated with heparin treated circuits, the first large scale multicenter clinical evaluation of heparin treated circuits was initiated in Europe. A common protocol of clinical outcome parameters was used and exclusion criteria were introduced to attempt to reduce the heterogeneity of the patient population. The overall target of the study was to investigate whether the use of heparin treated circuits in patients undergoing elective coronary artery surgery reduces postoperative morbidity and mortality in a large group of patients in distinct centers. In a subpopulation of patients in three centers extended biochemical studies were performed to evaluate the reduction of complement activation and leukocyte mediated inflammatory reaction in relation to clinical outcome. The results of this biochemical study are presented separately.

2. Patients and methods

Eleven European centers for cardiac surgery participated in the study. Between October 1993 and January 1995, in total 805 patients were enrolled up to a maximum of 100 per center. Eligible patients were candidates for elective coronary artery surgery (redo operation included), had left ventricular end diastolic pressure below 30 mm Hg or ejection fraction above 30%, and in case heparin was given preoperatively, activated clotting times <300 s. Excluded from the study were patients with simultaneous valve surgery, aneurysm surgery or other major surgery, any preoperative coagulopathy, previous cerebrovascular accident or ischemic attacks, chronic obstructive pulmonary disease, insulin dependent diabetes mellitus, renal insufficiency, hepatic insufficiency, active inflammatory disease or infection, or patients on anti-inflammatory drugs (except aspirin). These exclusion criteria were applied according to the definitions used in each participating center. Randomisation was done by envelope at the participating center, the physicians involved in postoperative patient care were blinded for randomisation. Informed consent was obtained from each patient and
ethical committee approval was obtained according to the policy of each center.

The extracorporeal circuit consisted of a soft-shell venous reservoir, roller pump, membrane oxygenator (Univox, Baxter Healthcare, Irvine, CA), cardiotomy reservoir and silicone or polyvinyl tubing system. Patients received either an untreated circuit or an identical but heparin treated circuit (from cannula to cannula, Duraflow®II, Bentley/Baxter, Uden, Netherlands) [14]. With regard to anaesthesia, priming procedures, perfusion circuits design (such as the inclusion of arterial line filters), perfusion techniques as well as surgical techniques, local policies were respected. After systemic heparinisation (300 IU/kg) was accomplished, CPB was initiated when the activated clotting time > 480 s. During CPB, activated clotting time was maintained > 480 s and additional heparin (in boluses of 5000 IU) was used when necessary. After termination of CPB, heparin was neutralised with protamine on a 1:1 ratio.

After the operation all patients were transferred to the intensive care unit (ICU) where they were managed according to local protocols. In addition to common patient characteristics and surgical data, the following variables were recorded: blood loss (chest tube drainage during the first 18 h postoperatively), the use of predonation (just before onset of CPB), pump blood return, autologous blood transfusion from chest tubes, and the need for blood products (cells and/or plasma). Postoperatively, a hematocrit value below 25% or haemoglobin level below 8 g/l were indicators for packed red cell transfusion. Cell savers were not used. The incidence of adverse events was defined as the occurrence of myocardial infarction, rethoracotomy, intra-aortic balloon pumping, rhythm disturbance, respiratory dysfunction, renal dysfunction, liver dysfunction, neurologic dysfunction, and mortality. Also, hours of mechanical ventilation in case patients were extubated within 24 h as well as ICU stay were measured.

3. Statistical analysis

Data were gathered on a case record form and stored in a central database. The BMDP statistical software package was used for analysis of the data. Differences between groups were assessed with two-sided t tests, Mann-Whitney U-test, or χ²/Fisher exact test when appropriate. Means are presented with standard deviation (S.D.), unless stated otherwise. A two-sided P < 0.05 was considered to be statistically significant. To analyse the effect of heparin treated circuits on adverse events and other categorical outcome variables, relative risks were estimated (with 95% confidence interval). Analysis of variance was used to detect differences in patient characteristics among centers.

Multiple logistic regression [1] was performed to compare both groups as to the following clinical endpoints: the need for blood products, mortality and morbidity. Morbidity was defined as the occurrence of either myocardial infarction, rethoracotomy for excessive bleeding, intra-aortic balloon pumping, renal dialysis or stroke. These outcome variables were compared between the groups (untreated vs. heparin treated circuits) with adjustment for the following variables: center, age, gender, previous infarction, ejection fraction, aspirin use, platelet count before CPB, body mass index, redo operation, aprotinin use, priming volume of the circuit, heparin dosage, protamine dosage, aortic cross clamp time, CPB time, lowest nasopharyngeal temperature during CPB, number of distal anastomoses, number of arterial grafts, and use of arterial grafts. Since the results of a multiple logistic regression analysis is in terms of odds ratio’s, these are presented together with a 95% confidence interval. In this presentation odds ratio’s may be interpreted as approximations for relative risks.

4. Results

From the 805 patients who were enrolled, 407 underwent CPB with untreated circuits (controls) and 398 with heparin treated circuits. Significant differences in patient characteristics were found between centers as indicated by the minimum and maximum values, but not between patients receiving heparin treated circuits and control circuits (Table 1). During the first 18 postoperative h, blood loss was not different between the groups (850 ml (S.D. 659) for controls vs. 911 ml (S.D. 663) for patients receiving heparin treated circuits, P = 0.41). There was no intergroup difference regarding hematocrit value and platelet count before and after surgery. The application of blood handling procedures like predonation, pump blood return and postoperative autotransfusion as well as the need for blood transfusions was equal among the groups, but varied widely among centers (Table 2).

Postoperative intubation time and intensive care stay are depicted in Figs. 1 and 2. Although there were no differences between patients receiving untreated circuits and those receiving heparin treated circuits, there was a wide variety among centers: mean intubation time ranged from 6.3 h (S.D. 4.1) from one center to 17.2 h (S.D. 3.4) in another center, while mean intensive care stay ranged from 1.1 days (S.D. 0.2) to 3.0 days (S.D. 1.1).

In total, 187 events occurred in the control group and 150 in the heparin treated circuit group. Apart from a lower incidence of postoperative intra-aortic balloon pumping (upper 95% confidence of relative risk 1.05) and rhythm disturbance without treatment (upper 95%
Table 1
Patient characteristics and surgical data

<table>
<thead>
<tr>
<th></th>
<th>Untreated (n = 407)</th>
<th>Heparin treated (n = 398)</th>
<th>Minimum for centers</th>
<th>Maximum for centers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
<td>Mean (S.D.)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.3 (9.5)</td>
<td>61.6 (9.2)</td>
<td>58.5 (9.4)</td>
<td>65 (9.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 (12)</td>
<td>79 (12)</td>
<td>75 (12)</td>
<td>84 (14)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 (8)</td>
<td>172 (8)</td>
<td>169 (9)</td>
<td>176 (7)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>57 (13)</td>
<td>59 (14)</td>
<td>51 (10)</td>
<td>67 (14)</td>
</tr>
<tr>
<td>Prime volume (ml)</td>
<td>1667 (412)</td>
<td>1656 (406)</td>
<td>983 (169)</td>
<td>2023 (302)</td>
</tr>
<tr>
<td>X-clamp time (min)</td>
<td>49 (23)</td>
<td>50 (25)</td>
<td>31 (10)</td>
<td>76 (33)</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>89 (37)</td>
<td>90 (41)</td>
<td>55 (20)</td>
<td>141 (49)</td>
</tr>
<tr>
<td>Distal anasthetic (NR)</td>
<td>3.3 (1.1)</td>
<td>3.3 (1.1)</td>
<td>2.7 (0.8)</td>
<td>3.8 (1.3)</td>
</tr>
<tr>
<td>Arterial anasthetic (NR)</td>
<td>1.1 (0.8)</td>
<td>1.1 (0.8)</td>
<td>0.7 (0.5)</td>
<td>2.8 (0.6)</td>
</tr>
<tr>
<td>Lowest temperature (°C)</td>
<td>29.4 (2.4)</td>
<td>29.4 (2.2)</td>
<td>26.4 (1.4)</td>
<td>31.2 (1.3)</td>
</tr>
<tr>
<td>Baseline ACT (s)</td>
<td>139 (42)</td>
<td>141 (52)</td>
<td>115 (28)</td>
<td>167 (61)</td>
</tr>
<tr>
<td>Total heparin (10³ IU)</td>
<td>32.1 (8.7)</td>
<td>31.1 (8.5)</td>
<td>27.1 (7.4)</td>
<td>35.7 (5.1)</td>
</tr>
<tr>
<td>Total protamine (mg)</td>
<td>285 (76)</td>
<td>292 (80)</td>
<td>196 (30)</td>
<td>345 (68)</td>
</tr>
<tr>
<td>ACT after protamine (s)</td>
<td>131 (29)</td>
<td>133 (29)</td>
<td>118 (19)</td>
<td>155 (44)</td>
</tr>
<tr>
<td>Gender (female) (%)</td>
<td>11</td>
<td>14</td>
<td>77</td>
<td>96</td>
</tr>
<tr>
<td>Preop infarct (%)</td>
<td>58</td>
<td>56</td>
<td>48</td>
<td>64</td>
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<tr>
<td>Preop aspirin (%)</td>
<td>70</td>
<td>70</td>
<td>39</td>
<td>92</td>
</tr>
<tr>
<td>Redo operation (%)</td>
<td>4.4</td>
<td>5.5</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Aprotinin (%)</td>
<td>16</td>
<td>13</td>
<td>0</td>
<td>93</td>
</tr>
</tbody>
</table>

confidence of relative risk 1.03), no intergroup differences in adverse events were found (Table 3). The overall mortality rate was 1.4%. In the control group, 7 patients died during the study period: 2 died of cerebrovascular accidents, 2 of myocardial infarction, 1 of cardiogenic shock, 1 of respiratory insufficiency, and 1 of pneumonia. In the group receiving heparin treated circuits, 4 patients died: 1 of myocardial infarction, 2 of cardiogenic shock and 1 of sepsis. During the course of the study no clinical or technical (patient or device related) side effects were registered.

The results of the logistic regression analysis are summarised in Table 4. Odds ratios were not significant, neither for the initial model (heparin treated circuits alone), nor after adjustments for explanatory variables. The incidence of morbidity was 46/407 in the control group vs. 38/398 in the heparin treated circuit group.

From the results in Table 4 it appeared that female gender and aortic cross clamp time (the number of distal anastomoses) contributed significantly to morbidity. Given this information, we additionally tested the hypothesis that the use of heparin treated circuits is beneficial in a subpopulation of females and a second subpopulation of patients with aortic cross clamp time longer than 60 min.

Females receiving control circuits needed more blood products (27/43, 63%) than those receiving heparin treated circuits (24/56, 43%; relative risk 0.68, 95% confidence interval 0.47–0.998). There was no difference in overall adverse events, although the incidence of rhythm disturbances (with or without treatment) was higher in females receiving control circuits (15/43, 35%) than in those receiving heparin treated circuits (9/55, 16%; relative risk 0.47, 95% confidence interval 0.23–0.97). In the heparin treated circuit group 11/53 (21%) of females were extubated within 6 h postoperatively whereas 2/43 (5%) of females in the control group ($P = 0.03$). The other outcome variables mentioned in Table 3 were not significantly different.

In the second subgroup of patients with aortic cross clamp times exceeding 60 min, patients receiving heparin treated circuits did not need IABP (0/93), whereas 5/104 (5%) of the patients in the control group needed IABP ($P = 0.06$). In the control group 27/104 (26%) of the patients were discharged from the ICU within 24 h after operation, whereas in the heparin treated circuit group 13/93 (14%) of the patients (relative risk 0.52, 95% confidence interval 0.29–0.94).

5. Discussion

The first European multicenter clinical evaluation of heparin treated circuits for elective coronary artery surgery revealed no overall difference in morbidity, mortality or blood usage in patients receiving these circuits in comparison to those receiving untreated circuits. However, subgroup analyses for female patients, and for patients requiring prolonged cross clamp times demonstrated beneficial effects of heparin treated circuits.

The enrolment of patients was guided by inclusion and exclusion criteria and resulted in a low-risk popula-
tion that underwent elective coronary artery surgery. In such a population, postoperative recovery with low morbidity and mortality rates can be expected. Consequently, the majority of patients could be extubated within 24 h postoperatively and discharged from the ICU on the first or second postoperative day. In such a low risk patient population larger groups are required to demonstrate significant clinical improvements with heparin treated circuits. To illustrate this, we calculated that a patient population of twice the size that was used in the present study would be required to reach a significant decrease in need for intra-aortic balloon pumping in the heparin treated circuit group (which then would result in a relative risk of 0.43, with 95% confidence interval 0.21–0.89).

From the logistic regression analysis it appeared that female gender contributed to postoperative morbidity and need for blood products. In this regard, female gender can be considered as a risk category in comparison to male gender. Subgroup analysis of this risk category demonstrated beneficial effects of heparin treated circuits with regard to blood use, incidence of rhythm disturbances and duration of mechanical ventilation. For patients with prolonged cross clamp times beneficial effects of heparin treated circuits were demonstrated as well. Whether other categories of patients, in whom the contribution of the inflammatory response to postoperative recovery may be more pronounced, could benefit also from heparin treated circuits deserves further investigation.

The effect of heparin treated circuits on complement activation has been demonstrated extensively [4,7,8,11,15,18,24,25]. However, the CPB procedure includes various sources of blood activation of which complement activation is only one. When blood is exposed to foreign surfaces, also the intrinsic clotting system, the fibrinolytic system and the kinin system (contact phase activation) become activated [26]. In addition to material dependent blood activation other sources of material independent blood activation can be identified. It has been demonstrated, that for instance, differences in perfusion techniques may also have a significant effect on blood activation during CPB and subsequently influence clinical outcome [11]. Hypoperfusion of the digestive tract during CPB induces intestinal mucosal ischemia and facilitates endotoxin transmigration from the intestine into the circulation [2,10]. Circulating endotoxins initiate the release and synthesis of inflammatory mediators like cytokines [6]. Although the contribution of endotoxin in the inflammatory response remains to be elucidated, normovolemic perfusion and reduced priming volumes have been identified as factors that can prevent endotoxin release [10,11]. One of the participating centers used low prime circuits and measured the effect on the pulmonary shunt postoperatively [19]. In the heparin treated circuit group postoperative pulmonary shunt was significantly lower than it was in controls. Under these circumstances the use of heparin treated circuits indeed resulted in truly improved organ function.

### Table 2

<table>
<thead>
<tr>
<th>Blood saving procedures</th>
<th>Untreated (% yes)</th>
<th>Heparin treated (% yes)</th>
<th>Minimum for centers (% yes)</th>
<th>Maximum for centers (% yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predonation</td>
<td>47</td>
<td>45</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Pump blood return</td>
<td>86</td>
<td>87</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Autotransfusion</td>
<td>49</td>
<td>53</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Donor blood use</td>
<td>31</td>
<td>34</td>
<td>7</td>
<td>61</td>
</tr>
</tbody>
</table>

Fig. 1. There was no significant difference (Mann-Whitney U-test) in duration of mechanical ventilation (horizontal axis) in patients receiving untreated circuits (dotted line) or heparin treated circuits (solid line).

Fig. 2. There was no significant difference (Mann-Whitney U-test) in duration of postoperative intensive care stay (horizontal axis) in patients receiving untreated circuits (dotted line) or heparin treated circuits (solid line).
Another source of blood activation that has been identified is blood-tissue contact within the pericardium. Pericardial shed blood is highly activated by tissue factor and tissue plasminogen activator from the pericardium [23]. Once this highly activated pericardial shed blood recirculates in the patient, it amplifies systemic blood activation. One of the participating centers routinely used aprotinin which inhibits fibrinolytic activity. Under these circumstances the use of heparin treated circuits also resulted in significantly improved clinical outcome [12].

6. Limitation of the study

Between the centers significant differences in patient characteristics were observed. Moreover, perfusion techniques such as prime volume/composition and blood handling procedures (predonation, pump blood return and postoperative autotransfusion) varied widely among the participating centers. Local treatment policies also determined the duration of mechanical ventilator support and duration of intensive care stay (data for centers not shown), which makes these outcome variables less powerful for the current study design. The variety in demographic parameters and the lack of standardisation resulted in a low-risk, and actually rather heterogeneous study population which makes it difficult to draw conclusions on outcome variables used in this setting.

In the present study no attempts were made to access the possible contribution of material independent blood activation sources to clinical outcome, nor any form of standardisation of these factors was introduced in the study protocol. Given, however, these additional potent sources of blood activation, it remains difficult to access the effect of only an isolated part of the material dependent blood activation aspects (the circuits) on clinical outcome. In fact, the distinct local treatment protocols in the present study tolerate potent material independent sources of blood activation that may vary widely among centers. Actually, the surfaces of the extracorporeal circuit was the only source of blood activation that was standardised in the present study.

7. Conclusion

In the current study group of elective low risk CABG patients, the application of heparin treated extracorporeal circulation circuits compared to untreated circuits did not result in statistical significant differences con-
cerning clinical outcome. Subgroup analyses, however, demonstrated significant improvements in clinical outcome for female patients and for patients requiring longer aortic cross clamp times. The results indicate that in such a multicenter clinical evaluation of low risk patients, the number of patients enrolled should be increased, and particularly patients at higher risk for cardiac surgery should be included. Both preoperative patient characteristics (i.e. risk stratification) as well as outcome variables (i.e. organ function) need to be better defined. In addition, other sources of blood activation (e.g. endotoxin translocation) need to be reduced, and patients CPB management protocols require more harmonisation amongst participating centers. In this way, the effect of heparin treated circuits in distinct patient categories and under optimised CPB management may be established for various organ systems.

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References


