Aspects of leucocyte and fat filtration during cardiac surgery
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CHAPTER 3

LEUCOCYTE FILTRATION OF RESIDUAL HEART LUNG MACHINE BLOOD IN CHILDREN UNDERGOING CONGENITAL HEART SURGERY

A. J. de Vries, Y. J. Gu, W. van Oeveren

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ABSTRACT

Cardiopulmonary bypass (CPB) leads to a generalized inflammatory reaction, resulting in increased postoperative leucocyte counts and decreased pulmonary function. In adults, removal of leucocytes from the residual heart-lung machine blood after CPB improved postoperative oxygenation. In children, however, the clinical effects of leucocyte filtration of the residual heart-lung machine blood are unknown. Therefore, we measured postoperative leucocyte counts and arterial blood oxygenation in children undergoing congenital cardiac surgery in a randomized prospective study. Anaesthesia and CPB were standardized. After CPB, the residual heart-lung machine blood was collected as usual. In a group of 25 children, this blood was filtered with a leucocyte depletion filter before transfusion. A control group of 25 children received this blood unfiltered. We found that the postoperative leucocyte counts were significantly lower in the filter group than in the control group ($p = 0.02$, repeated measurements ANOVA). This difference reached a maximum on the second postoperative day ($12.9 \times 10^9/L$ filter vs. $15.9 \times 10^9/L$ control, $p = 0.02$, Student’s $t$-test). Values for the arterial blood oxygenation on the first postoperative day were not different between both groups ($15.5 \pm 1$ kPa filter vs. $14.6 \pm 1.3$ kPa control, $p = 0.57$, Student’s $t$-test). We conclude that leucocyte filtration of the residual heart-lung machine blood reduced systemic leucocyte counts, but did not improve arterial blood oxygenation in children after congenital heart surgery.
INTRODUCTION

Cardiopulmonary bypass (CPB) leads to a systemic inflammatory reaction mainly through activation of complement and leucocytes, resulting in increased postoperative leucocyte counts and a decreased pulmonary function.\(^1\)\(^-\)\(^3\) In children, the inflammatory response to CPB tends to be more intense than in adults, because the surface of the CPB circuit in relation to the total body volume is larger.\(^4\) Moreover, this leucocyte-mediated inflammatory response initiated during CPB is likely to have a significant clinical impact, as a negative correlation between the expression of leucocyte adhesion molecules and postoperative oxygenation has been demonstrated recently in children.\(^5\)

Leucocyte filtration is a recently introduced technique to reduce a CPB-induced inflammatory response.\(^6\)\(^-\)\(^7\) Previously, we have shown in adults that leucofiltration of the residual heart-lung machine blood after CPB resulted in a reduced inflammatory response and improved lung function.\(^8\) In this study we examined the effect of leucofiltration of residual heart-lung machine blood on postoperative oxygenation and circulating leucocyte counts in children undergoing congenital heart surgery.

METHODS

After ethical committee approval and parent consent, 50 consecutive children who underwent congenital open-heart surgery were randomly divided into two groups. Procedures selected were correction for tetralogy of Fallot, simple closure of a ventricular septal defect, correction of atrioventricular septal defect, arterial switch operation for transposition of the great arteries and completion of the Fontan procedure. The power calculation for this study was based on the results of the partial oxygen pressure of the arterial blood (\(\text{PaO}_2\)) in our study in adults.\(^8\) The \(\text{PaO}_2\) on the first postoperative day was the primary end point for this study. It was therefore estimated that with an \(\alpha\) 0.05 and a \(\beta\) of 0.8, a total of 45 patients would be required to reach a statistically significant difference. Thus, in 25 children, the residual blood from the heart-lung machine after CPB was filtered with a leucocyte depletion filter before retransfusion. In a control group of 25 children this residual blood was retransfused unfiltered.

Anaesthesia was standardized and consisted of a midazolam and sufentanil infusion. Pancuroniumbromide was used for muscle relaxation. Ventilation was aimed at normocapnia with oxygen in air (\(\text{FiO}_2 = 0.4\)), a tidal volume of 6-10 ml.kg\(^{-1}\) and a positive end-expiratory pressure of 2-4 cmH\(_2\)O. CPB was instituted after heparin (300 IU/kg\(^{-1}\)) was given. The bypass circuit consisted of a double head roller pump (Stöckert, München, Germany) and a hollow fibre oxygenator (Dideco safe micro or Dideco 902, Sorin, Mirandola, Italy, depending on the size of the child). The flow during CPB was 2.4 L/m\(^2\) with moderate hypothermia (± 30°C). The priming solution consisted of human albumin 5% with 1000 IU heparin. If the calculated haemoglobin on bypass was less than 4.5 mmol/L, packed cells were added to the priming solution. After CPB and disconnection of the system, the residual blood in the heart-lung machine was collected in a transfusion bag, and retransfused in the child during wound closure and the first 2 hours in the intensive care unit (ICU). In the filter group this blood was filtered with one leucocyte depletion filter (Pall RS 1, Pall, Portsmouth,
GB) for each patient. Other filtration procedures (e.g. modified ultrafiltration) were not used.

We made the following measurements in the children. Leucocyte counts were performed after induction of anaesthesia and on the first four postoperative days. Platelet counts and the PaO₂ were determined after induction of anaesthesia, after arrival in the ICU and on the first postoperative day. In 10 children additional blood samples were taken from the residual heart-lung machine blood. In these samples leucocyte and platelet counts, and levels of haemoglobin and elastase, as a measure of leucocyte activation, were determined.

The statistical analysis was done as follows. For comparison of single data between the groups a two tailed Student’s t-test or the non-parametric Mann-Whitney test was used as appropriate. For the comparison of the groups for oxygenation, platelet and leucocyte counts on the different time points two way analysis of variance (ANOVA) for repeated measures was used to identify time, group and time-group interactions. To allow for multiple comparisons the Bonferroni adjustment was applied. Values are given as mean and standard error of the mean for normal distributed data, otherwise the median value and the 25 and 75 percentiles are given. A p-value ≤ 0.05 was considered significant.

RESULTS

The demographic data were similar in both groups (table 1). Intraoperatively, 270 ± 27 mL of residual heart-lung machine blood was collected in a transfusion bag after CPB. This corresponded with an index of 707 ± 50 mL/m². The composition of the residual heart-lung machine blood is shown in table 2.

The postoperative leucocyte counts increased over time (p < 0.001, figure 1), with a significant difference between the filter and the control group (p = 0.02). Postoperative platelet counts were not different between the groups (p = 0.11, repeated measurements ANOVA, table 3).

The PaO₂ values were similar in both groups (p = 0.43, repeated measurements ANOVA, table 3). However, to investigate if the underlying disease of the children influenced the postoperative PaO₂ values, we divided the children in a subgroup with a preoperative PaO₂ = <8.4 kPa and in a subgroup with a PaO₂ > 8.4 kPa. This arbitrary value paralleled the division in underlying cyanotic and non-cyanotic disease. The results, shown in table 4, indicate that in the cyanotic group (n = 28) the children in the filter and the control group had a similar postoperative PaO₂, whereas in the non-cyanotic group (n = 22) the children in the filter group had a slightly higher postoperative PaO₂.

The haemodynamic data at the end of the operation were not different (table 3). However to achieve that result dopamin (5-10 μg/kg/min) was used in 21 children in the control group vs. 11 in the filter group (p = 0.004) and isoprenalin (0.01-0.02 μg/kg/min) was used in 11 children in the control group vs. 2 in the filter group (p = 0.004). Blood loss during the first 24 hours was not different (table 3).
Table 1. Demographic data

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Filtration (n = 25)</th>
<th>Control (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closure of AV-canal</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Correction of Fallot</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Completion Fontan</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Arterial switch</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>VSD</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Age (month)</td>
<td>13 (2 - 31.5)</td>
<td>6 (1 - 28.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>0.42 (0.25 - 0.58)</td>
<td>0.36 (0.25 - 0.54)</td>
<td>0.50</td>
</tr>
<tr>
<td>CPB (min)</td>
<td>119 ± 8.7</td>
<td>126 ± 8.3</td>
<td>0.58</td>
</tr>
<tr>
<td>Intubation time (hour)</td>
<td>19 (9 - 48)</td>
<td>21 (16 - 54)</td>
<td>0.36</td>
</tr>
<tr>
<td>ICU stay (day)</td>
<td>1 (1 - 3.7)</td>
<td>2 (1 - 5)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>8 (7 - 11.7)</td>
<td>8 (7.5 - 13)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

AV, atrioventricular; VSD, ventricular septal defect; BSA, body surface area; CPB, cardiopulmonary bypass; ICU, intensive care unit

Table 2. Composition of the residual heart lung machine blood in 10 children

<table>
<thead>
<tr>
<th></th>
<th>Filtration (x10^9/L)</th>
<th>Control (x10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytes</td>
<td>5.1 ± 0.53</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (mmol/L)</td>
<td>4.5 ± 0.28</td>
<td></td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>141 ± 16</td>
<td></td>
</tr>
<tr>
<td>Elastase (ng.L⁻³)</td>
<td>70 ± 54</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Mean leucocyte counts before (pre-op) and after surgery for congenital heart disease (postoperative day 1, 2, 3 and 4) in children, that had the residual heart-lung machine blood filtered with a leucocyte depletion filter before retransfusion (filter), and in children, that had this blood retransfused unfiltered (control). The error bars represent the standard error of the mean. Repeated measurements analysis of variance revealed a significant difference over the time (p < 0.001) and between the two groups (p = 0.02)
**DISCUSSION**

Although the leucocyte depletion technology during cardiac surgery has repeatedly been reported in adults, only limited information is available in children. This study shows that in children undergoing cardiac surgery leucofiltration of residual heart-lung machine blood resulted in a prolonged reduction of postoperative leucocyte counts. However, in contrast to adult patients, this did not result in a difference in postoperative PaO₂.

There are at least two possible explanations for the difference between adults and children regarding the clinical effects. In the first place, we found high elastase values in the residual blood, which were about twice the values that we previously found in the residual heart-lung machine blood in adult patients. The elastase values reflect

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**Table 3. Clinical data**

<table>
<thead>
<tr>
<th></th>
<th>Filtration (n = 25)</th>
<th>Control (n = 25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenation (kPa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-op</td>
<td>11.4 ± 1.3</td>
<td>10.8 ± 1.3</td>
<td>0.77</td>
</tr>
<tr>
<td>Arrival ICU</td>
<td>16.7 ± 1.3</td>
<td>14.8 ± 1.3</td>
<td>0.36</td>
</tr>
<tr>
<td>Day 1 ICU</td>
<td>15.5 ± 1</td>
<td>14.6 ± 1.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Circulating platelet count (x10⁹.l⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-op</td>
<td>327 ± 18</td>
<td>380 ± 38</td>
<td>0.20</td>
</tr>
<tr>
<td>Arrival ICU</td>
<td>126 ± 10</td>
<td>154 ± 11</td>
<td>0.07</td>
</tr>
<tr>
<td>Day 1 ICU</td>
<td>162 ± 13</td>
<td>181 ± 13</td>
<td>0.31</td>
</tr>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrival ICU</td>
<td>140 ± 4</td>
<td>142 ± 3</td>
<td>0.79</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>Arrival ICU</td>
<td>55 ± 1.7</td>
<td>0.17</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>Arrival ICU</td>
<td>11.3 ± 0.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Blood loss (ml.m⁻²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>414 ± 68</td>
<td>324 ± 34</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Pre-op, pre-operative; ICU, intensive care unit; Day 1, the first postoperative day; AP, mean arterial pressure; CVP, central venous pressure

**Table 4. Postoperative partial oxygen pressure of the arterial blood in cyanotic and non-cyanotic children receiving leucocyte filtration**

<table>
<thead>
<tr>
<th>Preoperative PaO₂</th>
<th>&lt; 8.4 kPa</th>
<th>&gt; 8.4 kPa</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>filter (n = 14)</td>
<td>control (n = 14)</td>
<td>p-value</td>
<td>filter (n = 11)</td>
<td>control (n = 11)</td>
<td>p-value</td>
</tr>
<tr>
<td>Pre-op</td>
<td>6.7 ± 0.3</td>
<td>6.8 ± 0.4</td>
<td>0.9</td>
<td>17.2 ± 1.5</td>
<td>16.0 ± 2.0</td>
<td>0.63</td>
</tr>
<tr>
<td>Arrival ICU</td>
<td>15.6 ± 1.8</td>
<td>16.0 ± 2.1</td>
<td>0.88</td>
<td>17.7 ± 1.6</td>
<td>13.2 ± 1.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Day 1 ICU</td>
<td>14.4 ± 1.2</td>
<td>15.1 ± 1.9</td>
<td>0.76</td>
<td>17.0 ± 1.5</td>
<td>14.0 ± 1.7</td>
<td>0.21</td>
</tr>
</tbody>
</table>

PaO₂, partial oxygen pressure of the arterial blood; pre-op, preoperative; ICU, intensive care unit; Day 1, the first postoperative day
the degranulation of leucocytes and are associated with tissue injury. Thus, although
the number of leucocytes in the residual blood is somewhat lower than in adults,\textsuperscript{13} it is
likely that, after CPB, children have more activated leucocytes. Moreover, an increase
in leucocyte adhesion molecules has been demonstrated in children from the first to the
second postoperative day together with an increase in neutrophil counts, opposed to a
decrease in adhesion molecules and neutrophil counts in adults.\textsuperscript{14} This could explain
why we found a more prolonged effect of leucofiltration on leucocyte counts in
children than in adults, where the leucocyte counts on the first postoperative day were
similar in the filter group and in the control group.\textsuperscript{8} Second, the moment, or timing, of
leucocyte filtration during the operation may also play an important role in its clinical
significance and this could explain why we did not find an improvement in PaO\textsubscript{2}.
Children, especially children with cyanotic heart diseases have a low tolerance for free
oxygen radicals, and it is therefore likely that the damaging effects of activated
leucocytes occur in the initial reperfusion phase, immediately after aortic cross-clamp
release.\textsuperscript{9} This has also been shown as an increase in myeloperoxidase and lactoferrin,
as markers for leucocyte activation, immediately after aortic cross clamp release.\textsuperscript{15}
Thus in the children in the cyanotic group, with the large difference in pre- and
postoperative PaO\textsubscript{2} values, leucofiltration of the residual heart-lung machine blood
was too late to have an effect, which may explain why the postoperative PaO\textsubscript{2} values
in the filter and the control group were similar. In contrast, the children in the non-
cyanotic group, with no difference in pre- and postoperative PaO\textsubscript{2} values, had no
oxygen stress and thus in this small subgroup statistical significance in the
postoperative PaO\textsubscript{2} values between the filter and the control group was nearly
obtained. Currently, leucocyte depletion filters suitable for use in a paediatric
extracorporeal circuit are not available, which prevents earlier use of leucofiltration
during the operation. A paediatric arterial-line filter has been used, but was withdrawn
due to reported clotting in the CPB circuit distal to the filter\textsuperscript{10}. Thus, our strategy for
children may be too late for an effect on oxygenation, but sufficient for an effect on
leucocyte counts.

Although platelets are removed by leucocyte depletion filters,\textsuperscript{16} there was no
significant difference between the two groups regarding the postoperative platelet
counts. This finding may also explain that the postoperative blood loss was not
different between the two groups. The amount of retransfused residual blood in the
children, indexed on body surface, was comparable to that in the adult patients.\textsuperscript{8} We
transfused this blood during wound closure and the first 2 hours in the ICU. This was
not due to a flow limitation in the filter, but to the capacity of the child to accept the
transfused volume. For each patient we used one filter, which costs about 30 euro. However,
a larger study is necessary to assess if the use of these filters is cost-
effective.

An unexpected finding was that more inotropes were used in the control group.
This was transient, because on the first postoperative day this difference was not
present. Reduced inotropic support after leucofiltration has been described
previously.\textsuperscript{12,17} Our results support these findings and suggest that even leucofiltration
performed shortly after CPB results in a more stable haemodynamic profile.

Our study may be limited by the fact that we did not measure biochemical
parameters such as elastase or interleukins in the children. The measurement of
biochemical parameters would, of course, be helpful to gain insight in the effects of
leucocyte depletion, but, for the widespread application of a filtration strategy, it is necessary to obtain clinically useful results, which was on our primary clinical endpoint, an improved postoperative PaO$_2$ in the filter group, not the case in this study. A second limitation is the heterogenous patient group. We tried to minimise this by the selection of well described disease entities, and by a post hoc analysis of the effects of leucofiltration in cyanotic and non-cyanotic children. However, the pre- and postoperative PaO$_2$ should be interpreted with caution.

In conclusion, we found a significant reduction in leucocyte counts in children after corrective surgery for congenital heart disease by the transfusion of leucocyte depleted residual heart-lung machine blood. However, we did not find significant effects on postoperative oxygenation. Since the elastase levels in the residual heart-lung machine blood are high, and there is currently no suitable paediatric arterial in-line filter to achieve leucocyte depletion during CPB, the removal of leucocytes from this blood may offer an alternative to reduce the inflammatory reaction in children after congenital heart surgery.

REFERENCES
