Anticoagulation in severe sepsis and the multiple organ dysfunction syndrome

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Chapter 6

Pre-versus postdilution hemofiltration: a comparison of circuit thrombogenesis and efficacy

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Submitted
Abstract

Background
During continuous venovenous hemofiltration (CVVH), predilution can prolong circuit survival time, but the underlying mechanism has not been elucidated. Aim of the present study was to compare predilution to postdilution with respect to circuit thrombogenesis and efficacy.

Methods and Results
Eight critically ill patients were treated with both pre- and postdilution CVVH in a crossover fashion. Extracorporeal circuit pressures were measured hourly and samples of blood and ultrafiltrate were collected at five different timepoints. No signs of platelet activation or increased thrombin generation were found during either mode. Urea clearance was higher during postdilution, at the expense of higher circuit pressures. During postdilution, baseline platelet count and maximal prefilter pressure had a linear relationship, while both parameters correlated inversely with circuit survival time.

Conclusion
Pre- and postdilution CVVH did not differ in circuit thrombogenesis. During postdilution, urea clearance was higher and baseline platelet count was inversely correlated with circuit survival time.
Introduction

During the last decades, continuous venovenous hemofiltration (CVVH) has become the treatment of choice in critically ill patients needing renal replacement therapy. However, thrombosis in the extracorporeal circuit has always been a limiting factor [1]. Several systemically administered anticoagulants have been used to limit coagulation activation in the extracorporeal circuit, such as unfractionated and low molecular weight heparins, danaparoid, hirudin and nafamostat. However, the use of these anticoagulants is limited by the risk of bleeding. Another technique to limit thrombosis in the extracorporeal circuit is regional anticoagulation of the hemofilter, using either citrate before and calcium after the filter or heparin before and protamine after the filter. Citrate anticoagulation has recently gained popularity, although it carries the risk of metabolic disorders [2]. Regional anticoagulation using heparin and protamine carries the risk of protamine toxicity [3]. Historically, predilution has been suggested as another method to limit coagulation in the extracorporeal circuit, because it lowers hematocrit level, platelet count and concentration of coagulation factors in the hemofilter [4]. However, trials comparing predilution to postdilution are limited [5,6]. Moreover, the mechanisms by which predilution can prolong circuit survival time, have not been determined. Aim of the present randomized cross-over study was to compare predilution and postdilution with respect to extracorporeal circuit thrombogenesis and clearance.

Material and methods

Patients
The study was approved by the institutional review board and written informed consent was obtained from all participants or their authorized representatives. Critically ill adult patients with an indication for renal replacement therapy were eligible for the study. Exclusion criteria were recent bleeding, treatment with aspirin within one week before enrollment, treatment with therapeutic doses of unfractionated or low molecular weight heparin within 12 h before enrollment and results of routine coagulation tests such as protrombin time (PT) and activated partial thromboplastin time (APTT) exceeding twice the upper limit of normal.

Procedure
Eligible patients were randomly assigned to either predilution or postdilution for their first CVVH run. Twelve hours after a first run in predilution mode, the second was performed in postdilution mode and vice versa. To obtain vascular access, a double lumen catheter (Duo-Flow 400XL, 14F x 6” (15 cm), Medcomp, Harleysville PA, USA)
was inserted into a large vein (femoral, subclavian, or internal jugular vein). CVVH was performed using a Diapact hemofiltration machine (Braun AG, Melsungen, Germany) and a cellulose triacetate hemofilter (CT.190G, Baxter Healthcare Corp., Deerfield IL, USA). A bicarbonate buffered substitution fluid with a flow of 60 ml/min was used in both pre- and postdilution. The blood flow was set at 200 ml/min during postdilution and at 140 ml/min during predilution, to keep the total flow through the hemofilter constant at 200 ml/min in both modes. Ultrafiltration rate was preset at 60 ml/min and a negative fluid balance was allowed. Extracorporeal circuit pressures were measured every hour and limits were preset as follows: arterial pressure (PA): −200 mmHg, prefiltter pressure (PBE): 400 mmHg, transmembrane pressure (TMP): 450 mmHg. Circuit survival time was defined as the time during which the preset ultrafiltration rate was achieved, which implies that it was reached when automatic ultrafiltration rate reduction occurred, due to an elevated TMP.

**Anticoagulation**

The circuit was primed with 2 l NaCl 0.9%, to which 22800 IU of nadroparin (Sanofi-Synthelabo, Paris, France) were added. Before starting CVVH, a loading dose of 2850 IU nadroparin was administered intravenously, followed by a continuous prefiltter infusion of 456 IU/h.

**Blood and ultrafiltrate collection**

Blood was collected from the hemofiltration catheter before CVVH and from the extracorporeal lines immediately before and after the hemofilter at 0.5, 6, 12 and 18 h during CVVH. Ultrafiltrate was obtained at the same time points. Blood for the determination of hemoglobin, hematocrit, leukocyte and platelet counts was collected in K3-EDTA tubes and for the determination of urea in lithium heparin tubes. Blood for flow cytometry and coagulation assays was collected in 0.32% trisodium citrate and processed within 15 min. Plasma was prepared by centrifugation at 2500 g twice for 20 min at 16°C, followed by storage at −80°C until assays were performed.

**Laboratory assays**

PT and APTT were performed on an automated coagulation analyzer (Behring Coagulation System (BCS), Dade Behring, Marburg, Germany). Antithrombin activity was determined with Berichrom Antithrombin (Dade Behring) on a BCS. Thrombin-antithrombin complexes (TAT) and prothrombin fragment F1+2 (F1+2) were measured by ELISA (Dade Behring). Factor VII antigen levels were determined with an ELISA from Diagnostica Stago (Asnières-sur-Seine, France). For the flow cytometric measurements, we used a method adapted from Maquelin et al. [7]. Aliquots of 5 µl citrated blood were diluted in 35 µl N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES) buffer to
which 5 μl fluorescein isothiocyanate (FITC)-labeled anti-glycoprotein (GP) Ib and 5 μl of a second phycoerythrin (PE)-labeled monoclonal antibody were added: anti-CD62P (P-selectin) (Beckman Coulter, Miami FL, USA), anti-CD63 (GP53) (Beckman Coulter) and anti-fibrinogen (Biopool, Umeå, Sweden). After mixing and incubation for 30 min at room temperature in the dark, further staining was stopped by adding 2.5 ml HEPES buffer containing 0.3% paraformaldehyde. Flow cytometric measurements were performed in a FACSscan flow cytometer with CellQuest software (Becton Dickinson, San Jose CA, USA). Forward (FSC) and sideward (SSC) light scatter were set at logarithmic gain. Platelets were identified on FSC, SSC and binding of FITC-labeled anti-GP Ib. The surface expression of activation markers was determined in a population of 5000 platelets. The threshold for platelet activation was arbitrarily set at 2% with a PE-labeled IgG₁ control-antibody. All coagulation and flow cytometric results are reported without correction for the dilution used in the extracorporeal circuit.

Clearance calculations
Urea clearance was calculated at 0.5, 6, 12 and 18 h by using the following formula:

\[ UC = \text{urea}_{\text{UF}} \times \frac{\text{UF}}{\text{urea}_p}, \]

where UC is urea clearance (ml/min), \( \text{urea}_{\text{UF}} \) the urea level measured in the ultrafiltrate (mmol/l), UF the ultrafiltrate flow (ml/min) and \( \text{urea}_p \) the plasma urea level (mmol/l). The plasma urea level measured before the filter was used uncorrectedly for postdilution and multiplied by 200/140 for predilution, to correct for the dilution rate used. The decrease in plasma urea levels was compared for both modes. Again, the plasma level measured before the filter was used uncorrectedly for postdilution and multiplied by 200/140 for predilution.

Statistical analysis
Data were analyzed on an intention to treat basis, using the Statistical Package for the Social Sciences (SPSS) for Windows, version 11.0 (SPSS, Chicago IL, USA). Differences between pre- and postdilution were tested by analysis of repeated measures, using mixed linear models. Changes from baseline to a certain time point within the same group were analyzed by a paired student's t-test. Regression analysis was used to determine the influence of different parameters on circuit survival time. Values are given as mean ± SD or median and range if appropriate. Significance was defined as \( p<0.05 \).
Results

Patient characteristics
A total of 8 patients were enrolled in the study. Baseline patient characteristics are shown in Table 1 and baseline coagulation parameters in Table 2. Except for baseline platelet count, all baseline coagulation parameters were similar in both modes.

Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>8</td>
</tr>
<tr>
<td>Age</td>
<td>63 ±13</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Mean body weight (kg)</td>
<td>80 ± 19</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23 ± 8</td>
</tr>
<tr>
<td>Mechanical ventilation, n</td>
<td>6</td>
</tr>
<tr>
<td>Vasopressor use, n</td>
<td>6</td>
</tr>
<tr>
<td>Number of dysfunctional organ systems</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
</tr>
</tbody>
</table>

Data represent mean ± SD. APACHE, Acute Physiology and Chronic Health Evaluation.

Circuit survival time
In the 8 enrolled patients, 15 hemofiltration runs were performed, 8 in predilution and 7 in postdilution mode. In one patient, renal function recovered after the first hemofiltration run, obviating the need for a second run. Median circuit survival time during predilution was 28 h (range 10–44 h) and during postdilution 15 h (range 1–65 h) (p=0.74) (Figure 1). Four patients had their first run in predilution mode and four in postdilution mode. Median circuit survival time for the first run was 20 h (range 1–65 h) and for the second run 14 h (range 1–44 h) (p=0.61). Although not statistically significant, a greater number of hemofilters expired within one hour during postdilution (2 out of 7) compared with predilution (0 out of 8).
Table 2. Baseline coagulation parameters during pre- and postdilution

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Predilution</th>
<th>Postdilution</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline hematocrit (l/l)</td>
<td>0.30 ± 0.04</td>
<td>0.28 ± 0.04</td>
<td>0.69</td>
</tr>
<tr>
<td>PT (s)</td>
<td>14.9 ± 2.0</td>
<td>13.8 ± 1.9</td>
<td>0.22</td>
</tr>
<tr>
<td>APTT (s)</td>
<td>24 ± 5</td>
<td>22 ± 6</td>
<td>0.37</td>
</tr>
<tr>
<td>AT (%)</td>
<td>58 ± 13</td>
<td>67 ± 19</td>
<td>0.16</td>
</tr>
<tr>
<td>TAT (µg/l)</td>
<td>24.7 ± 25.2</td>
<td>30.4 ± 17.8</td>
<td>0.60</td>
</tr>
<tr>
<td>F1+2 (nmol/l)</td>
<td>1.86 ± 1.3</td>
<td>2.08 ± 1.5</td>
<td>0.78</td>
</tr>
<tr>
<td>FVII Ag (%)</td>
<td>55 ± 25</td>
<td>26 ± 30</td>
<td>0.12</td>
</tr>
<tr>
<td>Baseline platelet count (x 10⁹/l)</td>
<td>168 ± 100</td>
<td>109 ± 67</td>
<td>0.04</td>
</tr>
<tr>
<td>P-selectin expressing platelets (%)</td>
<td>5.1 ± 4.7</td>
<td>3.5 ± 2.1</td>
<td>0.37</td>
</tr>
<tr>
<td>GP53 expressing platelets (%)</td>
<td>4.9 ± 1.7</td>
<td>6.1 ± 2.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Fibrinogen expressing platelets (%)</td>
<td>3.2 ± 2.5</td>
<td>2.5 ± 0.6</td>
<td>0.34</td>
</tr>
</tbody>
</table>

PT, prothrombin time; APTT, activated partial thromboplastin time; AT, antithrombin; TAT, thrombin-antithrombin complex; F1+2, prothrombin fragment F1+2; FVII Ag, factor VII antigen, GP53, glycoprotein 53. Data represent mean ± SD.

![Figure 1](image.png)

**Figure 1.** Survival curve of CVVH circuits during pre- and postdilution. Survival of extracorporeal circuits during CVVH with predilution (dashed line) and postdilution (continuous line). CVVH, continuous venovenous hemofiltration.
**Hematocrit**
Predilution decreased the hematocrit from $0.30 \pm 0.04$ to $0.18 \pm 0.02$ ($p<0.0001$). Due to ultrafiltration, the hematocrit increased across the hemofilter to pre-procedure levels ($0.29 \pm 0.04$ vs $0.30 \pm 0.04$, $p=0.66$). During postdilution, the hematocrit increased across the hemofilter to approximately 1.4 times baseline ($0.38 \pm 0.08$ vs $0.28 \pm 0.05$, $p<0.005$). Hematocrit levels measured before the filter during the procedure were similar to those measured before the procedure ($0.30 \pm 0.04$ vs $0.28 \pm 0.04$ $p=0.65$).

![Figure 2](image.jpg)

**Figure 2.** Time course of PT and APTT during CVVH. Plasma levels of PT (upper panels) and APTT (lower panels) during predilution (left panels) and postdilution (right panels) measured before (○) and after the hemofilter (▲) after the administration of a bolus nadroparin at $t=0$, followed by a continuous infusion of nadroparin throughout $t=18$ h. Data represent mean ± SD. PT, prothrombin time; APTT, activated partial thromboplastin time; CVVH, continuous venovenous hemofiltration.
Clotting times
The time courses of PT and APTT values are depicted in Figure 2. During both pre- and postdilution, PT values increased significantly after administration of the nadroparin bolus, remaining significantly higher before the filter than after the filter (Figure 2). Similarly, APTT values increased significantly after administration of the nadroparin bolus in both pre- and postdilution. During predilution, the APTT value remained significantly higher before the filter than after the filter throughout the study period, whereas during postdilution, the APTT values both before and after the filter gradually returned to normal in the course of the study period (Figure 2).

![Figure 3](image_url)

**Figure 3.** Effect of pre- and postdilution CVVH on TAT levels. Plasma TAT levels during CVVH with predilution (left panel) and postdilution (right panel) measured before (○) and after the hemofilter (▲). Data represent mean ± SD. TAT, thrombin-antithrombin complex; CVVH, continuous venovenous hemofiltration.

Thrombin generation
In both modes, there was no significant change in TAT levels, neither across the hemofilter, nor over time, indicating that no activation of coagulation was observed (Figure 3). There was no significant change in levels of F1+2 either (data not shown).
Platelet counts
Because baseline values were higher in predilution mode, platelet counts were expressed as a percentage from baseline. During predilution, the platelet count measured before the filter decreased to $39 \pm 10\%$ baseline over 18 h ($p<0.001$), whereas measured after the filter, it decreased to $59 \pm 15\%$ baseline over 18 h ($p<0.005$). At all timepoints, platelet counts were significantly lower before the filter than after the filter ($p<0.001$). During postdilution, the platelet count measured before the filter did not change significantly over 18 h, whereas measured after the filter, the platelet count increased to $143 \pm 42\%$ baseline at $t=0.5$ h ($p=0.04$), without a significant change thereafter (Figure 4).

![Figure 4](image.png)

**Figure 4.** Effect of pre- and postdilution CVVH on platelet count. Platelet counts expressed as a percentage from baseline during CVVH with predilution (left panel) and postdilution (right panel) measured before (○) and after the hemofilter (▲). Data represent mean ± SD. CVVH, continuous venovenous hemofiltration.

Platelet activation
In both modes, there was no change in the percentage of platelets expressing GP53, neither across the hemofilter, nor over time (Figure 5). There was also no change in percentage platelets expressing either P-selectin or fibrinogen (data not shown). Thus, no signs of platelet activation were observed.
Extracorporeal circuit pressures
In Table 3, minimal and maximal pressures measured in the extracorporeal circuit are summarized for both modes. During postdilution, minimal levels of arterial, prefiler and transmembrane pressures were significantly higher than during predilution. Moreover, both minimal and maximal pressure drop over the hemofilter were significantly higher during postdilution. Interestingly, maximal transmembrane pressures were higher during predilution. All predilution runs were stopped because of ultrafiltrate reduction due to high transmembrane pressures. During postdilution, 3 out of 7 runs were stopped because of high arterial or prefiler pressures, and only 4 out of 7 runs because of ultrafiltrate reduction due to high transmembrane pressures.

![Graph](image)

**Figure 5.** Effect of pre- and postdilution CVVH on the percentage of GP53 expressing platelets. Percentage GP53 expressing platelets during CVVH with predilution (left panel) and postdilution (right panel) measured before (○) and after the hemofilter (▲). Data represent mean ± SD. CVVH, continuous venovenous hemofiltration; GP53, glycoprotein 53.
Table 3: Extracorporeal circuit pressures during pre- and postdilution

<table>
<thead>
<tr>
<th></th>
<th>Predilution</th>
<th>Postdilution</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA min (mmHg)</td>
<td>-27 ± 16</td>
<td>-73 ± 30</td>
<td>0.008</td>
</tr>
<tr>
<td>PA max (mmHg)</td>
<td>-85 ± 61</td>
<td>-159 ± 102</td>
<td>0.04</td>
</tr>
<tr>
<td>PBE min (mmHg)</td>
<td>134 ± 2</td>
<td>219 ± 87</td>
<td>0.02</td>
</tr>
<tr>
<td>PBE max (mmHg)</td>
<td>257 ± 38</td>
<td>283 ± 89</td>
<td>0.47</td>
</tr>
<tr>
<td>PV min (mmHg)</td>
<td>73 ± 14</td>
<td>119 ± 82</td>
<td>0.16</td>
</tr>
<tr>
<td>PV max (mmHg)</td>
<td>168 ± 45</td>
<td>152 ± 74</td>
<td>0.72</td>
</tr>
<tr>
<td>ΔP min (mmHg)</td>
<td>59 ± 21</td>
<td>84 ± 1</td>
<td>0.004</td>
</tr>
<tr>
<td>ΔP max (mmHg)</td>
<td>57 ± 20</td>
<td>88 ± 14</td>
<td>0.02</td>
</tr>
<tr>
<td>TMP min (mmHg)</td>
<td>35 ± 17</td>
<td>74 ± 11</td>
<td>0.001</td>
</tr>
<tr>
<td>TMP max (mmHg)</td>
<td>360 ± 50</td>
<td>228 ± 105</td>
<td>0.004</td>
</tr>
</tbody>
</table>

PA, arterial pressure; min, minimal; max, maximal; PBE, prefILTER pressure; PV, venous pressure; ΔP, pressure drop over the hemofilter; TMP, transmembrane pressure. Data represent mean ± SD.

Figure 6. Correlation between baseline platelet count and circuit survival time during CVVH in predilution (○) and postdilution (▲) mode. Data represent mean ± SD. CVVH, continuous venovenous hemofiltration.

Factors influencing circuit survival time

Baseline platelet count was inversely correlated with circuit survival time. This effect was significant for postdilution (p=0.02), but not for predilution (p=0.78) (Figure 6). Other baseline coagulation parameters did not correlate with circuit survival time. During postdilution, maximal prefILTER pressure was also inversely correlated with circuit
survival time ($r^2=0.73, p=0.01$). The relationship between baseline platelet count and maximal prefilter pressure during postdilution was linear ($r^2=0.93, p=0.001$) (Figure 7).

**Figure 7.** Correlation between baseline platelet count and PBE max during postdilutional CVVH. PBE max, maximal prefilter pressure. CVVH, continuous venovenous hemofiltration.

**Figure 8:** Plasma urea levels during pre- (○) and postdilution (▲). Data represent mean ± SD.
Urea clearance

In both modes, the calculated urea clearance did not change over time. During predilution, urea clearance at \( t=0.5 \) h was \( 46 \pm 10 \) ml/min compared with \( 51 \pm 3 \) ml/min at \( t=18 \) h \((p=0.46)\). During postdilution, the calculated urea clearance was \( 61 \pm 2 \) ml/min at both \( t=0.5 \) h and \( t=18 \) h \((p=0.75)\). Mean urea clearance was \( 61 \pm 2 \) ml/min during postdilution and \( 47 \pm 2 \) ml/min during predilution, which comes down to an overall 30% higher urea clearance during postdilution \((p<0.0001)\). In agreement with this finding, the decrease in mean urea level was greater during postdilution: 34% from 0–6 h, 25% from 6–12 h and 20% from 12–18 h, compared with 28% from 0–6 h, 10% from 6–12 h and 2% from 12–18 h during predilution \((p=0.03)\) (Figure 8).

Discussion

In the present cross-over study, pre- and postdilution did not differ with respect to extracorporeal circuit thrombogenesis. During postdilution however, minimal extracorporeal pressure levels were higher, and circuit survival time was inversely correlated with both baseline platelet count and maximal prefiltre pressure. Interestingly, a linear relationship between the latter two parameters was found. Finally, urea clearance was 30% higher during postdilution.

In two previous studies, predilution was associated with an increased circuit life. Uchino et al. found a median circuit life of 18 h during predilution, compared with 13 h during postdilution. In this study, predilution was a significant independent predictor of increased filter life, together with platelet count and heparin dose [5]. Van der Voort et al. found a median circuit survival time of 45.7 h during predilution, compared with 16.1 h during postdilution, using a method very similar to ours [6]. In the present cross-over study, the superiority of predilution with respect to circuit survival time could not be confirmed. However, the sample size of our study was small, carrying the risk of a type II error. Indeed, during postdilution, a relative high number of hemofilters (2 out of 7) expired within one hour, compared with none during predilution. Moreover, baseline platelet count was significantly lower in the postdilution group, which might have attenuated the difference in circuit survival time between pre- and postdilution.

We did not find evidence for thrombin generation in the extracorporeal circuit during either pre- or postdilution, as concentrations of both TAT and F1+2 did not change significantly, neither across the hemofilter nor over time. This finding is in contrast with the results of Cardigan et al., who found an increase in TAT levels over time in 8 out of 12 patients during hemofiltration, with an inverse correlation between the increase in TAT levels and circuit survival time [8].
No change in indicators of platelet activation was found, neither across the hemofilter, nor throughout the procedure. These findings confirm those of Kozek-Langenecker et al., who demonstrated that the extent of platelet activation as measured by the monoclonal antibodies PAC-1 and anti-CD62 remained constant during 24 h of hemofiltration [9]. The hypothesis that platelet activation plays a role in the initiation of thrombosis during hemofiltration, is supported by the fact that circuit survival time can be prolonged by adding prostaglandin I2 or E1 to the anticoagulation with unfractionated heparin [10]. In the present study however, no evidence for an influence of platelet activation on circuit survival time was found.

In the present study, minimal extracorporeal circuit pressures were higher during postdilution. During hemofiltration, the blood flow through the hollow fibers of the hemofilter is governed by the Hagen-Poiseuille equation: 

\[ Q_b = \frac{\Delta P}{8 \mu L/\pi r^4} \]

where \( Q_b \) is blood flow, \( \Delta P \) is pressure drop over the hemofilter, \( \mu \) is blood viscosity, \( L \) is hollow fiber length and \( r \) is hollow fiber radius [11]. As blood flow resistance (R) equals \( \Delta P/Q_b \), it is proportionate to blood viscosity, which is increased during postdilution, due to the increase in hematocrit [12]. To overcome the increased blood flow resistance in the hemofilter while maintaining a constant blood flow, the prefiltet pressure during postdilution increases. The pressure limit is more easily reached, causing the bloodpump to stop. Baldwin et al. demonstrated that interruptions of the blood flow are likely to promote clotting of the CVVH circuit. They nicely showed that the frequency of medium intensity (34–66%) flow reductions per hour was negatively correlated with filter life. Moreover, this correlation was much stronger than that seen with the anticoagulation variables normally monitored during CVVH [13]. High pressure circumstances entailing blood flow interruptions might have been the reason for shorter circuit survival times during postdilution in previous studies.

Interestingly, maximal transmembrane pressures were higher during predilution. Indeed, all predilution runs were terminated because of ultrafiltrate reduction due to high transmembrane pressures, whereas during postdilution, only half of the runs were terminated for this reason. During predilution, the lower pressure profile might allow the system to run long enough to be limited by protein accumulation in the filter micropores, leading to elevation of the transmembrane pressure.

During postdilution, we found an inverse correlation between circuit survival time and both baseline platelet count and maximal prefiltet pressure. Moreover, a linear relationship between the latter two parameters was demonstrated. The observed inverse correlation between circuit survival time and baseline platelet count during postdilution confirms our finding in a previous study [14]. To our knowledge however, this is the first time a linear relationship is demonstrated between baseline platelet count and maximal prefiltet pressure during postdilution. There are a few possible explanations for this phenomenon. First, platelet count has been shown to be an
independent denominator of blood viscosity [15]. Second, platelet cohesion is promoted by increased shear stress [16-18], which equals shear rate multiplied by viscosity. Shear rate is a measure of how rapid fluid layers are flowing past each other and equals dV/dr, where V is the fluid velocity and r is the hollow fiber radius. The shear rate is zero at the vessel center and maximal at the vessel wall. When blood flows through the hollow fibers of the hemofilter, platelets are pushed towards the wall, which increases both the local platelet concentration and the shear stress exerted on these platelets [16,18]. It is conceivable that a higher baseline platelet count facilitates the platelet cohesion induced by increased shear stress. Moreover, the increase in platelet count during postdilution might further potentiate platelet cohesion, leading to increased blood flow resistance and hence increased prefilter pressure.

In this study, overall urea clearance was 30% higher during postdilution. This finding confirms the results of Van der Voort et al. [6], who found a 36% higher creatinine clearance during postdilution (45 vs 33 ml/min). Our results also confirm the clearance calculation by David et al., who showed that the clearance of small solutes during predilution can be calculated by the formula: \( K = \frac{Q_b}{Q_b + Q_{inf}} \times Q_f \), where \( K = \text{clearance (ml/min)} \), \( Q_b = \text{blood flow rate (ml/min)} \), \( Q_{inf} = \text{infusion rate (ml/min)} \) and \( Q_f = \text{filtration rate (ml/min)} \) [19]. In our setting, the calculated clearance would be \( K = \frac{140}{200} \times 60 = 42 \text{ ml/min} \). Indeed, this value corresponds to the initial clearance we measured during predilution (46 ± 10 ml/min).

**Conclusion**

Pre- and postdilution did not differ with respect to extracorporeal circuit thrombogenesis. During postdilution, a 30% higher overall clearance was achieved at the expense of higher extracorporeal pressures. Circuit survival time during postdilution was inversely correlated with both baseline platelet count and maximal prefilter pressure and a linear relationship between the latter two parameters was demonstrated. This suggests that baseline platelet count has an important impact on maximal prefilter pressure and thus on circuit survival time during postdilution.
References

1. Abramson S, Niles JL. Anticoagulation in continuous renal replacement therapy. *Curr Opin Nephrol Hypertens* 1999;8:701-7