Predilution *Versus* Postdilution During Continuous Venovenous Hemofiltration: A Comparison of Circuit Thrombogenesis

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During continuous venovenous hemofiltration, predilution can prolong circuit survival time, but the underlying mechanism has not been elucidated. The aim of the present study was to compare predilution with postdilution, with respect to circuit thrombogenesis. Eight critically ill patients were treated with both predilutional and postdilutional continuous venovenous hemofiltration in a crossover fashion. A filtration flow of 60 ml/min was used in both modes. We chose blood flows of 140 and 200 ml/min during predilution and postdilution, respectively, to keep the total flow through the hemofilter constant. Extracorporeal circuit pressures were measured hourly, and samples of blood and ultrafiltrate were collected at five different time points. Thrombin-antithrombin complexes and prothrombin fragments F1 + 2 were measured by ELISA, and platelet activation was assessed by flow cytometry. No signs of thrombin generation or platelet activation were found during either mode. During postdilution, baseline platelet count and maximal prefilter pressure had a linear relation, whereas both parameters were inversely related with circuit survival time.

In summary, predilution and postdilution did not differ with respect to extracorporeal circuit thrombogenesis. During postdilution, baseline platelet count and maximal prefilter pressure were inversely related with circuit survival time. *ASAIO Journal* 2006; 52:416–422.

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 the activation of coagulation 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 with the use of 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 with postdilution are limited.[5,6] Moreover, the mechanisms by which predilution can prolong circuit survival time have not been determined. The aim of the present randomized crossover study was to compare predilution with postdilution, with respect to extracorporeal circuit thrombogenesis.

Materials 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 1 week before enrollment, treatment with therapeutic doses of unfractionated or low-molecular-weight heparin within 12 hours before enrollment, and results of routine coagulation tests such as prothrombin 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. After finishing a first run in predilution mode, the second was performed after an interval of 12 hours in postdilution mode and vice versa. To obtain vascular access, a double-lumen catheter (Duo-Flow 400XL, 14F × 6 inches (15 cm), Medcomp, Harleysville, PA, USA) was inserted into a large vein (femoral, subclavian, or internal jugular vein). CVVH was performed with the use of a Diapact hemofiltration machine (Braun AG, Melsungen, Germany) and a cellulose triacetate hemofilter (CT.190G, Baxter Health Care Corp., Deerfield, IL, USA). A bicarbonate-buffered substitution fluid with a flow of 60 ml/min was used in both predilution 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

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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 mm Hg, prefilter pressure (PBE): 400 mm Hg, transmembrane pressure (TMP): 450 mm Hg. Circuit survival time was defined as the time during which the preset ultrafiltration rate was achieved, that is, when extracorporeal circuit pressures exceeded the preset pressure limits, leading to automatic reduction of the ultrafiltration rate, this was considered as an end point.

Anticoagulation

The circuit was primed with 2 l NaCl 0.9%, to which 22,800 IU of nadroparin (Sanofi-Synthelabo, Paris, France) was added. Before starting CVVH, a loading dose of 2850 IU nadroparin was administered intravenously, followed by a continuous prefilter 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 hours 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 minutes. Plasma was prepared by centrifugation at 2500*g* twice for 20 minutes at 16°, 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, Dade Behring, Marburg, Germany). Antithrombin activity was determined with Berichrom Antithrombin (Dade Behring) on a Behring Coagulation System. 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 minutes 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 FACScan 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-GPIb. 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 IgG_1 control antibody. All coagulation and flow cytometric results are reported without correction for the dilution used in the extracorporeal circuit, unless stated otherwise.

Correction of Laboratory Values for Hemoconcentration Across the Hemofilter

To assess the actual change in levels of TAT, F1 + 2, and platelet count across the hemofilter, values measured at the filter inlet were corrected for hemoconcentration across the hemofilter by using a correction factor, based on ultrafiltration rate (Qf) and hematocrit (Ht). Taking into account that TAT levels were measured in plasma, we used the following formula to correct TAT levels for hemoconcentration across the hemofilter:

$$TAT_{corr} = TAT_{pre} \times \frac{200(1 - Ht_{pre})}{140(1 - Ht_{post})}$$

where TAT_{corr} is the TAT value corrected for the hemoconcentration across the hemofilter, TAT_{pre} is the TAT value at the hemofilter inlet, Ht_{pre} is the Ht at the hemofilter inlet, and Ht_{post} is the Ht at the hemofilter outlet. The amount of fluid entering the filter inlet per minute (200 ml) is multiplied by the plasma fraction ($1 - Ht_{pre}$) to obtain the amount of plasma in which TAT_{pre} was measured, and this value is divided by the plasma fraction to which the amount of fluid was concentrated across the hemofilter [$140\ (1 - Ht_{post})$]. To correct levels of F1 + 2, a similar formula was used.

As platelet counts were measured in whole blood, we used the following formula to correct platelet counts for hemoconcentration across the hemofilter:

$$platelets_{corr} = platelets_{pre} \times \frac{200}{140}$$

where $platelets_{corr}$ the concentration of platelets corrected for hemoconcentration across the hemofilter and $platelets_{pre}$ is the concentration of platelets at the filter inlet.

Clearance Calculations

The filter clearance of urea was calculated at t = 0.5, 6, 12, and 18 hours, using the following formula:

$$Kf_{urea} = \frac{urea_{UF} \times UF\ \ volume}{urea_{before\ filter}}$$

where Kf_{urea} is the filter clearance of urea (in ml/min), $urea_{UF}$ is the urea concentration in the ultrafiltrate (in mmol/l), UF volume is the volume ultrafiltrated in (ml/min), and $urea_{before\ filter}$ is the uncorrected concentration of urea in the fluid entering the hemofilter (in mmol/l).

The filter extraction of urea Ef_{urea} was calculated by dividing the filter clearance of urea Kf_{urea} by the actual filter flow of 200 ml/min in both predilution and postdilution:

$$Ef_{urea} = \frac{Kf_{urea}}{200} = \frac{urea_{UF} \times UF\ \ volume}{200 \times urea_{before\ \ filter}}$$

The extracorporeal urea clearances K_{expost} for postdilution and K_{expre} for predilution were calculated by multiplying the filter extraction Ef_{urea} by the actual blood flow (200 ml/min for

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Table 1. Baseline Patient Characteristics

Characteristic	No.
Total	8
Age	63 ±13
Male sex (%)	3 (38)
Mean body weight (kg)	80 ± 19
APACHE II score	23 ± 8
Mechanical ventilation	6
Vasopressor use	6
No. of dysfunctional organ systems	4 ± 1
Clinical settings	
Infectious disease	6
Cardiac surgery	1
Heart failure	1

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

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postdilution and 140 ml/min for predilution):

$$K_{\text{expost urea}} = \frac{\text{urea}_{\text{UF}} \times \text{UF volume}}{\text{urea}_{\text{before filter}}}$$

$$K_{\text{expre urea}} = \frac{140 \times \text{urea}_{\text{UF}} \times \text{UF volume}}{200 \times \text{urea}_{\text{before filter}}}$$

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). Differences between predilution 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 medians and range if appropriate. Significance was defined as $p < 0.05$.

Results

Patient Characteristics

A total of eight 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.

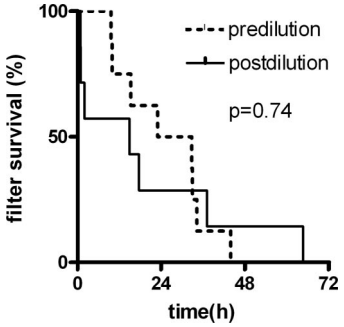

Figure 1. Survival of extracorporeal circuits during predilution *(dashed line)* and postdilution *(continuous line)*.

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 hours (range, 10 to 44 hours) and during postdilution 15 hours (range, 1 to 65 hours) (NS) (**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 hours (range, 1 to 65 hours) and for the second run, 14 hours (range, 1 to 44 hours) (NS). Although not statistically significant, a greater number of hemofilters expired within 1 hour during postdilution (2 of 7) compared with predilution (0 of 8).

Hematocrit

Predilution decreased the hematocrit from 0.30 ± 0.04 to 0.18 ± 0.02 ($p < 0.001$). As the result of ultrafiltration, the hematocrit increased across the hemofilter to preprocedure levels (0.29 ± 0.04 *vs.* 0.30 ± 0.04, NS). During postdilution, the hematocrit increased across the hemofilter to approximately 1.4 times baseline (0.38 ± 0.08 *vs.* 0.28 ± 0.05, $p < 0.01$). Hematocrit levels measured before the filter during the procedure were similar to those measured before the procedure (0.30 ± 0.04 *vs.* 0.28 ± 0.04, NS).

Table 2. Baseline Coagulation Parameters During Predilution and Postdilution

Characteristic	Predilution	Postdilution	*p* Value
Baseline hematocrit (l/l)	0.30 ± 0.04	0.28 ± 0.04	NS
PT (s)	14.9 ± 2.0	13.8 ± 1.9	NS
APTT (s)	24 ± 5	22 ± 6	NS
AT (%)	58 ± 13	67 ± 19	NS
TAT (μg/l)	24.7 ± 25.2	30.4 ± 17.8	NS
F1 + 2 (nmol/l)	1.86 ± 1.3	2.08 ± 1.5	NS
FVII Ag (%)	55 ± 25	26 ± 30	NS
Baseline platelet count (x10^9/l)	168 ± 100	109 ± 67	< 0.05
P-selectin–expressing platelets (%)	5.1 ± 4.7	3.5 ± 2.1	NS
GP-53–expressing platelets (%)	4.9 ± 1.7	6.1 ± 2.8	NS
Fibrinogen-expressing platelets (%)	3.2 ± 2.5	2.5 ± 0.6	NS

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

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Table 3. Maximal and Minimal Values of Coagulation Parameters During Predilution and Postdilution

Characteristic	Predilution		Postdilution	
	Before filter	After filter	Before filter	After filter
PT min (s)	14.9 ± 2.0	14.1 ± 2.6	13.8 ± 0.1	12.1 ± 0.7
PT max (s)	20.4 ± 3.6*‡	15.7 ± 1.9§	15.9 ± 2.0*§	13.9 ± 1.4
APTT min (s)	24 ± 5	32 ± 4	22 ± 6	25 ± 4
APTT max (s)	58 ± 13*‡	37 ± 8‡	41 ± 10†‡	31 ± 8‡
TAT min (μg/l)	10 ± 7.6	14.5 ± 10.5	15.2 ± 7.1	20.4 ± 10.2
TAT max (μg/l)	24.7 ± 25.2	29.2 ± 15.7	30.4 ± 17.8	46.1 ± 20.4
F1 + 2 min (nmol/l)	0.7 ± 0.6	1.2 ± 1.0	1.7 ± 0.9	2.5 ± 1.7
F1 + 2 max (nmol/l)	1.9 ± 1.3	1.6 ± 1.1	2.6 ± 2.0	4.8 ± 4.7
Platelet count min (% baseline)	39 ± 10*‡	59 ± 15‡	100 ± 0	100 ± 0
Platelet count max (% baseline)	100 ± 0	91 ± 11	125 ± 43§	182 ± 83
GP-53–expressing platelets min (%)	4.9 ± 1.7	4.9 ± 1.3	6.1 ± 2.8	6.1 ± 3.5
GP-53–expressing platelets max (%)	7.4 ± 3.5	6.2 ± 2.6	8.8 ± 4.9	9.0 ± 4.8

* Before *versus* after filter, $p < 0.01$.
† Before *versus* after filter, $p < 0.05$.
‡ *Versus* baseline, $p < 0.01$.
§ *Versus* baseline, $p < 0.05$.
PT indicates prothrombin time; APTT, activated partial thromboplastin time; TAT, thrombin-antithrombin complex; F1 + 2, prothrombin fragment F1 + 2; GP-53 glycoprotein 53. Data represent mean ± SD.

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Clotting Times

During both predilution and postdilution, PT values increased significantly after administration of the nadroparin bolus, remaining significantly higher before the filter than after the filter (**Table 3**). Similarly, APTT values increased significantly after administration of the nadroparin bolus in both predilution and postdilution. During predilution, the APTT value remained significantly higher before the filter than after the filter throughout the study period ($p < 0.01$), whereas during postdilution, the APTT values both before and after the filter gradually returned to normal in the course of the study period.

Thrombin Generation

In both modes, there was no significant change in levels of TAT and F1 + 2, neither across the hemofilter, nor over time, indicating that no activation of coagulation was observed (**Table 3**). When levels of TAT and F1 + 2 were corrected for hemoconcentration across the hemofilter, there was no significant difference between the values measured at the filter outlet and the values corrected for hemoconcentration across the hemofilter, indicating the absence of thrombin generation across the hemofilter.

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% ± 10% baseline over 18 hours ($p < 0.01$), whereas measured after the filter, it decreased to 59% ± 15% baseline over 18 hours ($p < 0.01$). At all time points, platelet counts were significantly lower before the filter than after the filter ($p < 0.01$). When platelet counts were corrected for hemoconcentration across the hemofilter, actually measured platelet counts at the hemofilter outlet during predilution were significantly lower than predicted, based on hemoconcentration occurring across the hemofilter. During postdilution, the platelet count measured before the filter did not change significantly over 18 hours, whereas measured after the filter, the platelet count increased to 143% ± 42% baseline at t = 0.5 hours ($p < 0.05$), without a significant change thereafter. When platelet counts were corrected for hemoconcentration across the hemofilter, actually measured platelet counts at the hemofilter outlet during postdilution were not significantly different from the platelet counts predicted, based on hemoconcentration across the hemofilter.

Platelet Activation

In both modes, there was no change in the percentage of platelets expressing GP53, neither across the hemofilter, nor over time (**Table 3**). 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 4**, minimal and maximal pressures measured in the extracorporeal circuit are summarized for both modes. During

Table 4. Minimal and Maximal Pressures Measured in the Extracorporeal Circuit

	Predilution	Postdilution	*p* Value
PA min (mm Hg)	–27 ± 16	–73 ± 30	<0.01
PA max (mm Hg)	–85 ± 61	–159 ± 102	<0.05
PBE min (mm Hg)	134 ± 2	219 ± 87	<0.05
PBE max (mm Hg)	257 ± 38	283 ± 89	NS
PV min (mm Hg)	73 ± 14	119 ± 82	NS
PV max (mm Hg)	168 ± 45	152 ± 74	NS
ΔP min (mm Hg)	59 ± 21	84 ± 1	<0.01
ΔP max (mm Hg)	57 ± 20	88 ± 14	<0.05
TMP min (mm Hg)	35 ± 17	74 ± 11	0.001
TMP max (mm Hg)	360 ± 50	228 ± 105	<0.001

PA indicates 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.

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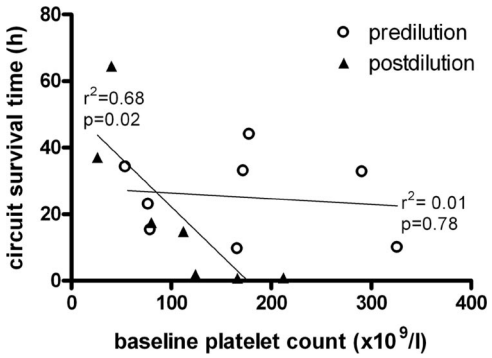

Figure 2. Correlation between baseline platelet count and circuit survival time during hemofiltration in predilution (○) and postdilution (▲) mode. Data represent mean ± SD.

postdilution, minimal levels of arterial, prefilter, 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 of 7 runs were stopped because of high arterial or prefilter pressures and only 4 of 7 runs because of ultrafiltrate reduction due to high transmembrane pressures.

Factors Influencing Circuit Survival Time

Baseline platelet count was inversely related with circuit survival time. This effect was significant for postdilution ($p < 0.05$) but not for predilution (**Figure 2**). Other baseline coagulation parameters did not correlate with circuit survival time. During postdilution, maximal prefilter pressure was also inversely related with circuit survival time ($r^2 = 0.73$, $p = 0.01$). The relation between baseline platelet count and maximal prefilter pressure during postdilution was linear ($r^2 = 0.93$, $p = 0.001$) (**Figure 3**).

Urea Clearance

Mean urea filter clearance during both predilution and postdilution was constant over time, ranging from 62.5 ± 13.8 ml/min at t = 0.5 hours to 67.1 ± 3.5 ml/min at t = 18 hours during predilution and from 59.8 ± 1.9 at t = 0.5 hours to 59.9 ± 2.6 ml/min at t = 18 hours during postdilution. There was no statistically significant difference in mean filter clearance between the two modes. Mean filter extraction ratios were 32 ± 0.02 and 30 ± 0.01 in predilution and postdilution, respectively. Extracorporeal clearances were 44.6 ± 2.9 and 60.4 ± 1.7 ml/min for predilution and postdilution, respectively ($p < 0.01$).

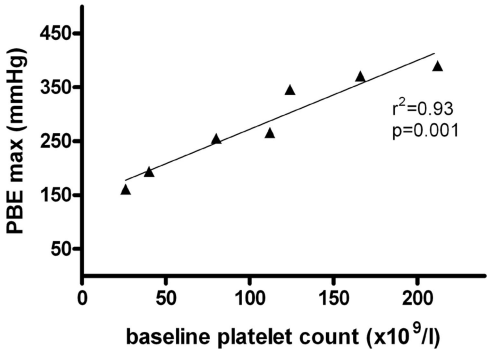

Figure 3. Correlation between baseline platelet count and maximal prefilter pressure (PBE max) during postdilutional hemofiltration.

Discussion

In the present crossover study, predilution 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 related with both baseline platelet count and maximal prefilter pressure. Interestingly, a linear relation between the latter two parameters was found.

In two previous studies,[5,6] predilution was associated with an increased circuit life. Uchino *et al.*[5] found a median circuit life of 18 hours during predilution, compared with 13 hours during postdilution. In this study, predilution was a significant independent predictor of increased filter life, together with platelet count and heparin dose. Van der Voort *et al.*[6] found a median circuit survival time of 45.7 hours during predilution, compared with 16.1 hours during postdilution, using a method very similar to ours. In the present crossover 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 of 7) expired within 1 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 predilution and postdilution.

During postdilution, the mean hematocrit increased across the hemofilter from 0.28 ± 0.05 to 0.38 ± 0.08 ($p < 0.01$), whereas during predilution, the diluted mean hematocrit of 0.18 ± 0.02 at the hemofilter inlet increased to 0.29 ± 0.04 at the hemofilter outlet ($p < 0.01$). However, this hemoconcentration across the hemofilter did not result in thrombogenesis, as no significant increase in levels of TAT and F1 + 2 was detected during either mode, neither across the hemofilter, nor over time. These results confirm the results of Stefanidis *et al.*,[8] who did not find a significant difference in fibrinopeptide A and TAT complexes between patients with a hematocrit >30% and patients with a hematocrit <30% during postdilution hemofiltration. However, the present findings are in contrast with the results of Cardigan *et al.*,[9] who found an increase in TAT levels over time in 8 of 12 patients during hemofiltration, with an inverse relation between TAT levels and circuit survival time.

During postdilution, platelet counts increased significantly at t = 0.5 hours, remaining constant thereafter. There was no significant difference in actually measured and predicted platelet counts at the hemofilter outlet, based on hemoconcentration across the hemofilter. During predilution, however, platelet counts measured both before and after the filter decreased significantly over time. Moreover, actually measured

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platelet counts at the hemofilter outlet were significantly lower than predicted, based on hemoconcentration across the hemofilter. The reason for this disproportionate decrease in platelet count during predilution is unclear.

No change in indicators of platelet activation was found, either across the hemofilter, or throughout the procedure. These findings confirm those of Kozek-Langenecker *et al.*,[10] who demonstrated that the extent of platelet activation, as measured by the monoclonal antibodies PAC-1 and anti-CD62, remained constant during 24 hours of hemofiltration. 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.[11] In the present study, however, no evidence for an influence of platelet activation on circuit survival time was found.

In the design of the present study, total flow across the hemofilter was kept constant at 200 ml/min in both modes, because we anticipated thrombogenesis to be proportionate to prefilter pressure and thus to flow rate across the hemofilter, based on the results of earlier studies. However, despite the equal flow across the hemofilter in both predilution and postdilution, 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: $Qb = \Delta P/(8\ \mu L/\pi r^4)$, where Qb is blood flow, ΔP is pressure drop over the hemofilter, μ is blood viscosity, L is hollow fiber length, and r is hollow fiber radius.[12] As blood flow resistance (R) equals $\Delta P/Qb$, it is proportionate to blood viscosity, which is increased during postdilution, due to the increase in hematocrit.[13] To overcome the increased blood flow resistance in the hemofilter while maintaining a constant blood flow, the prefilter pressure during postdilution increases. The pressure limit is more easily reached, causing the blood pump to stop. Baldwin *et al.*[14] 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% to 66%) flow reductions per hour was inversely related with filter life. Moreover, this correlation was much stronger than that seen with the anticoagulation variables normally monitored during CVVH.[14] 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 relation between circuit survival time and both baseline platelet count and maximal prefilter pressure. Moreover, a linear relation 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.[15] To our knowledge, however, this is the first time a linear relation has been demonstrated between baseline platelet count and maximal prefilter 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.[16] Second, platelet cohesion is promoted by increased shear stress,[17–19] which equals shear rate multiplied by viscosity. Shear rate is a measure of how rapidly 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 toward the wall, which increases both the local platelet concentration and the shear stress exerted on these platelets.[17,19] 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, mean extracorporeal urea clearance was 60.4 $\pm$ 1.7 ml/min during postdilution and 44.6 $\pm$ 2.9 ml/min during predilution. This difference was expected, as an ultrafiltration rate of 60 ml/min was used during both predilution and postdilution, whereas a higher blood flow was used during postdilution (200 *vs.* 140 ml/min). Thus, according to the clearance calculation by David *et al.*,[20] the anticipated urea clearance was 60 ml/min during postdilution and 42 ml/min during predilution (60 $\times$ 140/200). We found a higher urea clearance than expected during predilution, which may be explained by the fact that in the predicted clearance, we did not take into account hematocrit, plasma protein content, and equilibrium distribution coefficient between red cells and plasma. Indeed, lower values of hematocrit and total plasma protein content and a higher urea gradient between red cells and plasma yield a higher urea clearance. David *et al.*[20] reported a 6% higher clearance when these factors are taken into account. In the present study, the measured extracorporeal urea clearance was indeed 6% higher than calculated (44.6 $\pm$ 2.9 *vs.* 42 ml/min). Determination of the optimal blood flow and substitution rate, to obtain the highest clearance at the lowest rate of filter obstruction during predilution, remains a challenge for future studies.

The impact of enhanced urea clearance on platelet function during postdilution is unclear, as the influence of uremia on platelet function is complex. Decreased thromboxane A2 production, abnormal intracellular calcium mobilization, increased intracellular cyclic AMP and cyclic GMP and abnormal aggregability have all been described in uremic platelets and may all contribute to defective platelet function in uremic patients.[21] In the present study, we studied only three markers of platelet activation: P selectin, GP53, and fibrinogen. We did not find a difference in the three activation markers studied during either predilution or postdilution. Apparently, the enhanced urea clearance during postdilution did not influence the studied markers of platelet activation. However, the influence of enhanced urea clearance on other determinants of platelet function was not studied.

Conclusion

Predilution and postdilution did not differ with respect to extracorporeal circuit thrombogenesis. During postdilution,

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extracorporeal circuit pressures were significantly higher and circuit survival time was inversely related with both baseline platelet count and maximal prefilter pressure. Moreover, a linear relation 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. For predilution, additional studies are needed to determine the optimal blood flow and substitution rate to obtain the highest clearance at the lowest rate of filter obstruction.

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