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Influence of hematocrit on hemostasis in continuous venovenous hemofiltration during acute renal failure

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Influence of hematocrit on hemostasis in continuous venovenous hemofiltration during acute renal failure.

Background. Hematocrit plays a major role in primary hemostasis by influencing blood viscosity and platelet adhesion. During continuous venovenous hemofiltration (CVVH), it is suspected that an increased hematocrit is accompanied by an activation of hemostasis and frequently leads to thromboses in the extracorporeal system. In order to examine this hypothesis, we studied the influence of hematocrit on hemostasis during CVVH.

Methods. Fourteen patients (8 men and 6 women, mean age 65 ± 10 years) with acute renal failure undergoing CVVH were prospectively enrolled. Polysulfone hemofilters (AV 600®; Fresenius, Oberursel, Germany) were used in all of the patients; blood flow rates were adjusted to 120 ml/min. No blood products and coagulation-related medication, except unfractionated heparin, were applied. Study exclusion criteria included a history of thromboembolism and artificial heart valves. Hemostasis activation markers (fibrinopeptide A, thrombin-antithrombin III complex, β-thromboglobulin, platelet retention) and hematocrit values were determined before and at three-day intervals during the course of CVVH treatment.

Results. The mean hematocrit value ($\bar{X}$ ± SEM) was 29 ± 1% (range, 22 to 35%). Patients with hematocrit values of less than 30% ($N = 7$) were compared with patients with higher hematocrit values (>30%, $N = 7$). The patients with a lower hematocrit (<30%) showed a stronger activation of hemostasis during CVVH when compared with those with a higher hematocrit (>30%), as indicated by a tendency toward higher values for fibrinopeptide A (25 ± 8 vs. 14 ± 5 ng/ml, $P = 0.35$), thrombin-antithrombin III complex (15 ± 4 vs. 10 ± 2 ng/ml, $P = 0.66$), and a higher β-thromboglobulin/creatinine ratio (0.62 ± 0.17 vs. 0.48 ± 0.12, $P = 0.8$).

Conclusion. Contrary to our hypothesis, hematocrit values of more than 30% are not accompanied by an increased hemostasis activation during CVVH. Concerning hemostasis activation, hematocrit values between 30 and 35% may be suitable for patients on CVVH.

Continuous arteriovenous hemofiltration (CAVH) was reported by Kramer et al in 1977 as a continuous treatment modality for patients with acute renal failure [1]. Since then, various other regimens for continuous renal replacement therapy, for example, continuous venovenous hemofiltration (CVVH), have been developed. CVVH is especially suitable in patients with water and electrolyte imbalances that are hemodynamically unstable [2]. The latter advantage and its ability to treat uremia effectively, even in cases of hypercatabolism, have led to the rapid spread of this modality in recent years [3].

Bleeding represents an important morbidity and mortality factor in acute renal failure (ARF), and therefore, changes in hemostasis during CVVH may influence the prognosis of ARF [4, 5]. The continuous contact between blood and thrombogeneic foreign materials (hemofilter, extracorporeal circulation system), inherent in CVVH, activates the coagulation cascade, necessitating intravenous anticoagulation treatment. These factors may lead to pronounced alterations in hemostasis during CVVH.

Hematocrit plays a major role in primary hemostasis by influencing blood viscosity and platelet adhesion [6]. It is therefore suspected that higher hematocrit values may lead to a more pronounced activation of hemostasis and more frequent thromboses in the extracorporeal system during CVVH [7]. The objective of this study is to determine whether changes in hemostasis (plasmatic coagulation, platelets) that occur during CVVH are influenced by variations of hematocrit values.

METHODS

We prospectively examined 14 patients (8 men and 6 women, mean age 65 ± 10 years) with acute renal failure of varying origin (Table 1) who were undergoing CVVH treatment in an intensive care unit. Patients with preexisting disseminated intravascular coagulation (DIC), venous thrombosis, arterial and pulmonary embolism, or thrombosis, and patients with artificial heart valves were excluded from the study. The patients received no coagulation-related medication except heparin during CVVH. Fibrinopeptide A, thrombin-antithrombin III

Key words: blood coagulation, CVVH, platelet function, thrombosis, water and electrolytes, hemodynamics.

Table 1. Profiles of patients undergoing continuous venovenous hemofiltration

Case No.	Age	Sex	Diagnosis	Days on CVVH	DIC	Bleeding	Outcome
1	79	f	Cerebral hemorrhage	7	−	−	Died
2	71	m	Pneumonia	19	−	+	Died
3	71	f	Cholangitis	16	−	−	Died
4	65	f	Cerebral hemorrhage	4	−	−	Died
5	69	m	ACVB operation[a]	29	−	−	Died
6	50	m	Heart failure	7	−	−	Survived
7	61	f	Septic shock	11	−	−	Died
8	66	m	Pneumonia, ARDS[b]	3	−	−	Died
9	74	m	ACVB[a] operation	9	−	−	Survived
10	45	m	Pneumonia	12	−	+	Survived
11	60	m	Septic shock	6	−	−	Survived
12	81	m	Cardiogenic shock	5	−	+	Died
13	51	f	Pneumonia	3	−	−	Died
14	61	f	Cardiogenic shock	9	−	−	Died
Mean	65			10.0			
SD	10			7.2			

[a] Aortocoronary venous bypass
[b] Adult respiratory distress syndrome

complex, β-thromboglobulin, and platelet retention were determined before and at three-day intervals during treatment. Patients with hematocrit values of less than 30% ($N = 7$) were compared with patients with higher hematocrit values (>30%, $N = 7$).

A standardized CVVH technique was employed in all patients. Percutaneously introduced double-lumen venous catheters (Shaldon catheters, 1.8 mm diameter) were used for vascular access (internal jugular, subclavian as femoral vein). The filters used were polysulfone hemofilters with a filtration surface of 1.35 m^2 (AV 600®; Fresenius, Oberursel, Germany). Blood flow rates were adjusted to approximately 120 ml/min with substitution fluid administration in a postdilution mode. Filtration rates were approximately 20 ml/min in order to maintain urea concentrations at approximately 20 mmol/liter. An unfractionated heparin (Liquemin®; Roche, Basel, Switzerland) was used as anticoagulant. Low-dose heparin was administered intravenously in all patients (500 IU/hr) before the initiation of CVVH treatment. During CVVH, the heparin dosage was adjusted via the activated clotting time (ACT) with a target ACTs of more than 110 seconds.

Blood samples for coagulation tests were collected in polypropylene tubes (Sarstedt, Nümbrecht, Germany) containing citrate (one part sodium citrate 3.8% and 9 parts blood) and centrifuged at 3000 *g* for 15 minutes at 4°C to obtain platelet-poor plasma (cPPP). Blood samples for β-thromboglobulin determinations were collected in glass tubes with CTAD (citrate, theophylline, adenosine, dipyridamole) as the anticoagulant. Enzyme-linked immunosorbent assay (ELISA) was used to determine fibrinopeptide A, β-thromboglobulin (Boehringer, Mannheim, Germany), and thrombin-antithrombin III complex (Behringwerke, Marburg, Germany) plasma concentrations [8, 9]. Whole blood was taken and processed immediately with Adeplat S glass bead filters (Semmelweis, Milan, Italy) to determine Hellem II platelet retention [10]. Platelet counts were performed before and after being filtered with the differences (retention) expressed as a percentage of the total platelet count before filtering (reference 60% to 99%). The reduction of platelet retention indicates an impaired platelet adhesiveness [11]. The remaining plasmatic coagulation tests were performed with a ball coagulometer (KC 10; Amelung, Lemgo, Germany) or a digital photometer (6114 S; Eppendorf, Hamburg, Germany). ACT was measured immediately after blood sampling with an ACTester® (Trimed, Huntington, CA, USA). The whole blood count and the hematocrit from ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood (1 mg EDTA/ml blood) was determined with an electronic cell counter (System 900; Serono Diagnostics, Freiburg, Germany).

If not otherwise indicated, data are expressed as mean values ± SEM ($\bar{X} \pm$ SEM). The probability of error for comparison of the measured values was calculated using the Wilcoxon signed rank test for paired data and the Mann–Whitney *U*-test for unpaired data. The interdependence of the different variables was checked by means of a Pearson correlation analysis.

RESULTS

Fibrinopeptide A (33 ± 6 ng/ml, reference <3.0) and thrombin-antithrombin III complex (11 ± 1.5 ng/ml, reference 1.0 to 4.0) concentrations were elevated before initiation of CVVH, and no further rise of these parameters could be observed during CVVH treatment. Platelet retention, which was reduced prior to CVVH (39 ± 10%, reference 60 to 99), fell to 16 ± 6% after CVVH, whereas

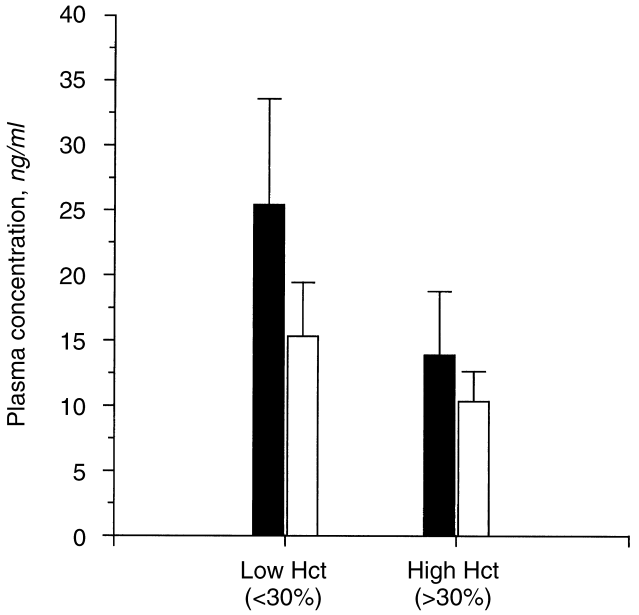

Fig. 1. Plasmatic coagulation parameters [(■) fibrinopeptide A, (□) thrombin-antithrombin III complex] during treatment by continuous venovenous hemofiltration (CVVH) in patients ($N = 7$) with low hematocrit values (<30%) compared with patients ($N = 7$) with high hematocrit values (>30%). The values are plotted as mean and SEM ($\bar{X} \pm$ SEM).

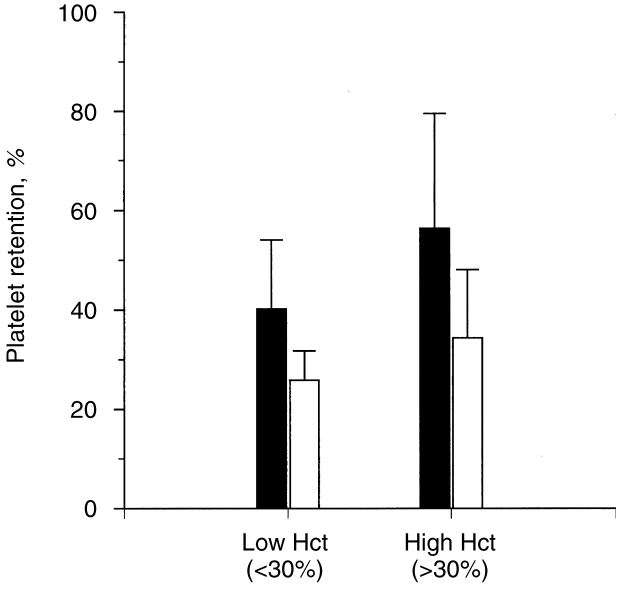

Fig. 2. Platelet retention before (■) and during (□) treatment by continuous venovenous hemofiltration (CVVH) in patients ($N = 7$) with low hematocrit values (<30%) compared with patients ($N = 7$) with high hematocrit values (>30%). The values are plotted as mean and SEM ($\bar{X} \pm$ SEM).

β-thromboglobulin/creatinine ratios (reference 0.23 to 0.41) increased from 0.39 ± 0.06 before to 0.64 ± 0.18 after CVVH.

Antithrombin III concentrations were slightly lower than normal (17.4 ± 3.5 U/ml, reference 18 to 23), and the fibrinogen concentrations were higher than normal (565 ± 138 mg/dl, reference 200 to 450) before commencement of CVVH.

Hemoglobin values (range, 76 to 125 g/liter) and hematocrit (range, 22 to 35%) were decreased in all patients. Patients with a lower hematocrit (<30%, $N = 7$) showed increased fibrinopeptide A (25 ± 8 vs. 14 ± 5 ng/ml, $P = 0.35$) and thrombin-antithrombin III complex (15 ± 4 vs. 10 ± 2 ng/ml, $P = 0.66$) concentration during CVVH treatment when compared with patients with a higher hematocrit (>30%, $N = 7$), without reaching statistical significance (Fig. 1).

Intercomparison of patients with hematocrit values less than 30% and patients with higher hematocrit values (>30%) also showed no significant difference in platelet retention (26 ± 6 vs. 34 ± 14%, $P = 0.7$). β-Thromboglobulin/creatinine ratios (0.62 ± 0.17 vs. 0.48 ± 0.12; $P = 0.8$) were not significantly different during CVVH treatment in both groups (Figs. 2 and 3).

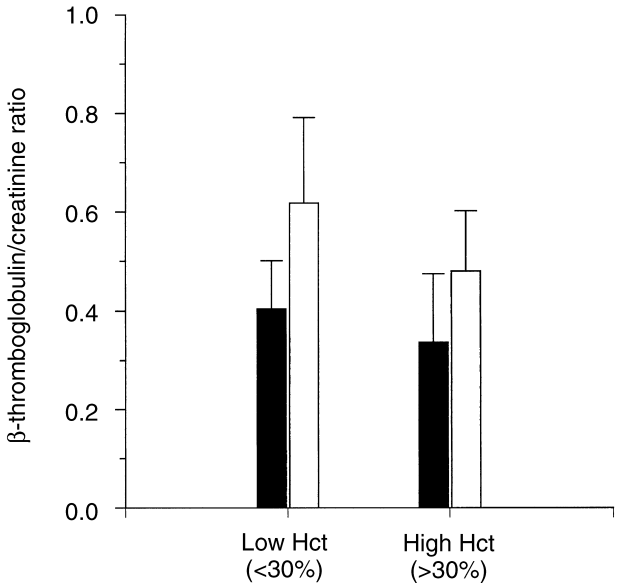

Fig. 3. Ratio of β-thromboglobulin/creatinine before (■) and during (□) treatment by continuous venovenous hemofiltration (CVVH) in patients ($N = 7$) with low hematocrit values (<30%) compared with patients ($N = 7$) with high hematocrit values (>30%). The values are plotted as mean and SEM ($\bar{X} \pm$ SEM).

DISCUSSION

Uremia influences hemostasis in acute renal failure, inducing uremic thrombocytopathy, and DIC is a frequent complication of multiorgan failure [12–14]. Furthermore, renal replacement therapy by CVVH may influence hemostasis in different ways. Blood contact with foreign materials (for example, hemofilters, blood tubes) and with air (for example, in the venous bubble trap)

may activate coagulation. In addition, there are major perturbations and mechanical damage of blood cells by the pump (shear stress). A study of the resultant hemostatic alterations in patients with acute renal failure poses a difficult problem.

The contact between blood and thrombogeneic foreign materials during CVVH has already been shown to induce a pronounced platelet activation [15]. An increase of hematocrit is accompanied by an enhancement of blood viscosity, of platelet adhesion, and probably of shear stress, and thereby may strongly contribute to the observed activation of hemostasis. Furthermore, as demonstrated in clinical and experimental studies, increasing hematocrit contributes to thrombosis development in various clinical settings [16, 17].

The aim of this study was to determine whether hematocrit value variations affect hemostasis (plasmatic coagulation, platelets) during CVVH. We therefore compared hemostasis activation in patients with a lower hematocrit ($<30\%$, $N = 7$) and patients with a higher hematocrit ($>30\%$, $N = 7$).

Our results showed that, contrary to our expectations, a higher hematocrit was not associated with a significant difference in the activation of the plasmatic coagulation. This was true before as well as during CVVH treatment.

There is a pronounced activation of coagulation (hypercoagulability) with enhanced plasmatic coagulation marker levels (fibrinopeptide A, thrombin-antithrombin III complex) in all patients prior to CVVH. As previously discussed, this hypercoagulability is probably inherent to uremia and is apparently independent of the DIC or the blood contact with foreign materials (abstract; Boisclair et al, *Thromb Haemost* 69:778, 1993) [18].

The connection between hematocrit and primary hemostasis (platelets, endothelium) was first reported by Duke in 1910 in his classic description of bleeding time. From his observation that bleeding time is prolonged in anemia, Duke postulated an influence of the erythrocytes on bleeding time [19]. Furthermore, the influence of increasing hematocrit on platelet function, for example, after erythropoietin therapy, has been demonstrated by *in vitro* and *in vivo* studies of patients on chronic hemodialysis [20, 21].

The lack of any significant difference in platelet activation during CVVH between patients with lower ($<30\%$) and higher ($>30\%$) hematocrit values is an unexpected finding. Theoretically, hematocrit should strongly influence platelet function during CVVH because of the increased blood viscosity and increased platelet adhesion associated with higher hematocrit values. This study is limited by the fact that hematocrit values in all patients were below 35%. A hematocrit dependence of platelet activation may probably become apparent with hematocrit values higher than 35 to 40%.

In conclusion, hematocrit values of greater than 30% up to 35% were not accompanied by an increased hemostasis activation either before or during the CVVH treatment. These results suggest that, concerning hemostasis activation, hematocrit values can be safely maintained between 30 and 35% in patients with acute renal failure on CVVH.

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