Heparin Use in Continuous Renal Replacement Procedures: The Struggle Between Filter Coagulation and Patient Hemorrhage[1]

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ABSTRACT

Heparin is the most widely used anticoagulant in continuous renal replacement procedures but little is known about the balance between filter coagulation and patient hemorrhage during treatment. Filter survival and hemorrhagic complications during 240 filter periods in 78 critically ill patients, treated with continuous arteriovenous hemofiltration and hemodiafiltration, were studied for this article. The crude incidence of filter coagulation was 17.7 ± 2.5 (mean ± SE) per 1000 h at an activated partial thromboplastin time (APTT) of 15 to 35 s, as determined in systemic blood samples. The incidence of filter coagulation gradually decreased to 9.0 ± 2.7 per 1000 h at an APTT of 45 to 55 s ($P = 0.031$). The crude incidence of patient hemorrhage was 2.9 ± 1.0 per 1000 h at an APTT of 15 to 35 s and increased almost threefold to 7.4 ± 2.4 per 1000 h when the APTT was 45 to 55 s ($P = 0.009$). There was no difference in filter survival between treatment with hemofiltration only and hemodiafiltration. Mean survival of acrylonitrile filters (33.8 ± 4.3) was significantly lower compared with the survival of polyamide filters (104.1 ± 14.4 h, $P = 0.003$). After adjustment for the type of the filter, mean arterial blood pressure, and platelet count, the risk for filter coagulation decreased 25% (relative risk, 0.77; 95% confidence interval (CI), 0.62 to 0.96) for every 10-s increase in APTT. At the same time, the risk for patient hemorrhage increased 50% (relative risk, 1.57; 95% CI, 1.43 to 1.72). The occurrence of filter coagulation or hemorrhages were not correlated with the administered dose of heparin. Concurrent use of coumarin derivatives had a positive effect on filter survival, without increasing the overall incidence of hemorrhages. It was concluded that the systemic APTT is a good predictor of the risk for filter coagulation and patient hemorrhage. Safety and efficacy of heparin therapy seems optimal at an APTT between 35 and 45 s.

Key Words: *Hemofiltration, heparin, APTT, filter survival, patient hemorrhage*

Since the introduction of continuous techniques for renal replacement in critically ill patients, the method has been hampered by coagulation of the filters, necessitating frequent exchange of systems. Heparin is used almost exclusively to prevent filter coagulation and to prolong filter survival (1). Notwithstanding the widespread use, the data supporting such a beneficial effect of heparin on filter survival are scarce, whereas the use of heparin in critically ill patients, often devoid of hemostatic platelets and coagulation factors, can lead to major bleeding complications (2–8). Few studies have addressed the delicate balance of filter coagulation and patient hemorrhage, and their aggregated data do not provide guidelines for daily practice (3,5). This absence has resulted in a wide variety of anticoagulant dose regimens. This variation also existed within our hospital. Therefore we were able to study the effects of heparin during continuous renal replacement therapy on the maintenance of filters and hemorrhagic complications with special emphasis on concurrent risk factors.

PATIENTS AND METHODS

Patients

From January 1991 through August 1994, 85 patients with acute renal failure in the intensive care units of the departments of Internal Medicine, General Surgery, and Thoracic Surgery of the University Hospital of Leiden were treated either with continuous arteriovenous hemofiltration or continuous arteriovenous hemodiafiltration (CAVH/DF).

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All treatments were supervised by the Department of Nephrology. Clinical data were retrieved by a scrupulous review of the medical records and the dialysis journals. In seven patients, the data were insufficient for a detailed reconstruction of the treatment and these cases were excluded from the analysis. A total of 240 filter periods in 78 patients were reviewed. Table 1 shows the characteristics of the patients and the primary causes of renal failure.

Continuous Arteriovenous Hemofiltration and Hemodiafiltration

CAVH/DF was performed via venous and arterial femoral cannulae (VasCath HFS 10 cm × 8 French and 10 cm × 10 French respectively, VasCath Incorporated, Mississaugo, Ontario, Canada), by using polyamide filters (Gambro FH66D, Gambro Dialysatoren GmbH&Co, Hechingen, Germany) or acrylonitrile filters (Hospal AN69 HF Multiflow 60, Hospal Industry, Meyzieu, France), depending on the free choice of the dialysis nurse. All filters were primed with 3 L of normal saline containing 10,000 U heparin (unfractioned high-molecular weight heparin). At the initiation of the procedure 2,000 U heparin was administered intravenously unless the activated partial thromboplastin time (APTT) was spontaneously prolonged (twofold normal values), or the patient was treated with coumarin derivatives, or when severe thrombocytopenia was present ($<50 \times 10^9$/L). Ultrafiltration was aimed at 700 to 1000 mL/hr without use of a pump, but by manipulating the height between filter and collection bag. Substitution fluid was always administered before the filter (predilution technique) and adjusted every hour to achieve the desired fluid balance. If clearance of small molecular substances was thought to be insufficient, dialysis fluid was pumped countercurrent to blood flow. Dialysis flow was fixed at 999 mL/h. Heparin was continuously administered at the arterial side of the filter and titrated on the APTT in systemic blood samples, which was determined at least every 6 h. The intended value of the APTT was 40 to 50 s, two times the normal value. In patients treated with coumarin derivatives, the intended value of the international standardized prothrombin time (INR) was 3.0 to 4.5 (normal value = 1).

End Points

Coagulation of the filter was defined as visible clot-forming at the inlet and outlet of the filter or in the lines, together with a more than 50% decrease in ultrafiltration rate. In all other cases, it was noted as "no coagulation." Filter survival was noted in hours. The definition of hemorrhage was derived from Levine *et al.* (9). Hemorrhage was considered as "major" if the bleeding occurred intracranially, retroperitoneally, or resulted in death or in the replacement of 2 or more U of blood within 24 h. All other hemorrhagic events were considered to be "minor."

For each filter period, the type of filter and simultaneous treatment with other anticoagulant therapy was recorded. For 39 filters, the type of filter was unknown. The following parameters, which may be related with coagulation and hemorrhage, were scored every 6 h: heparin dose (in U/h), APTT (in s), and mean arterial blood pressure (in mm Hg). In addition, transient decreases in mean arterial blood pressure of more than 20% were numbered every 24 h. The platelet count was determined every 24 h. All of these parameters were also ascertained at the moment when filters were disconnected and at the moment that hemorrhagic complications occurred. The timing of the hemorrhage was determined with a clinician's eye: for example, when an unexplained decrease in blood pressure occurred, followed several hours later by melena, the start of hemorrhage was assumed to be the moment of the decrease in blood pressure and not the moment of the appearance of melena.

Statistical Analysis

The crude incidence of filter coagulation and patient hemorrhage was calculated for patients on heparin only and for patients on concurrent therapy with coumarin derivatives separately. For each filter, the APTT values in time fluctuated around the target value and were assumed to be constant for 6 h after determination. The APTT values were classified in four strata of APTT values: a normal APTT (15 to 35 seconds), one and one-half times prolonged (35 to 45 s), two times prolonged (45 to 55 s), and more than two times prolonged (>55 s). The end points (numerator) were classified according to the most recent APTT stratum. Every period of 6 h treatment (denominator) was grouped according to the APTT strata and summed for all filters. Crude incidence rates (end points/total treatment time) in the various APTT strata were compared with Poisson regression. We used the likelihood ratio statistic to test for trends over the various categories. Mean filter survival was determined with Kaplan-Meier estimates for each of the two types of filters and for CAVH and

TABLE 1. Primary cause of renal failure, mean age, and outcome in 78 patients treated with continuous renal replacement therapy

Number of Patients	Primary Cause of Renal Failure	Mean Age (Range)	Deaths (Percentage)
25	Sepsis complicated by MODS[a]	53 (15 to 78)	14 (56)
24	Forward failure after cardiac surgery	62 (23 to 79)	21 (88)
12	Complication of acute abdominal aortic surgery	60 (42 to 75)	9 (75)
6	Connective tissue disorders/vasculitides	48 (30 to 64)	4 (67)
3	Myocardial infarction	69 (63 to 73)	1 (33)
8	Miscellaneous	48 (17 to 70)	4 (50)
78	All patients	56 (15 to 79)	53 (68)

[a] MODS, Multiple Organ Dysfunction Syndrome.

CAVHDF apart. Differences in survival were evaluated with the log-rank test.

To obtain risk estimates for filter coagulation and patient hemorrhage, adjusted for several risk factors, a Cox's proportional hazards model was used. In this analysis, the patients who were treated with coumarin derivatives were excluded. The type of filter was entered as a time-independent covariate. The values of APTT, heparin dosage, mean arterial blood pressure, decreases in blood pressure, and platelet count differed during treatment. Therefore, these variables were entered as time-dependent covariates, *i.e.*, the variables have different values during the analysis of a filter. Because multiple filters were used with one patient, repetitive observations of filter coagulation and hemorrhage may be dependent on the underlying patient characteristics. We tested for heterogeneity of filter-survival and hemorrhage-free interval between patients, *i.e.* testing the hypothesis that the event occurred irrespective of the patients characteristics, with the goodness of fit-test for Cox's proportional hazards models (Verwey PJM, van Houwelingen HC, Stijnen T: A goodness-of-fit test for Cox's proportional hazards model based on martingale residuals, submitted). Data are presented as mean ± SE and 95% CI were calculated. A P value < 0.05 was considered statistically significant.

RESULTS

Total Numbers of Filters and Complications

A total of 240 filters in 78 patients during 11,760 h of renal replacement therapy were evaluated. The distribution of filters with relation to the type of treatment is shown in Table 2. Some 141 filters (59%) were disconnected because of coagulation of the extracorporeal system, whereas the other 99 filters (41%) were disconnected because of transport of the patient to the operating room or diagnostic procedures outside the intensive care units. Fifty filters were used in patients who were treated with coumarin derivatives, amounting to a total of 3,036 h.

A total of 48 hemorrhagic complications occurred in 37 patients, of which 40 were major and 8 were minor (Table 3). In almost all cases, major bleeding along the intravascular catheters was accompanied by bleeding along other inserted drains (thoracic or abdominal). The hemorrhagic complications occurred proportional in the several patient groups except for the acute abdominal aortic surgery group, where only two bleeding episodes were observed.

Three patients died as a result of hemorrhages: none of them were using coumarin derivatives. One patient died of an intracranial hemorrhage (diagnosed by CT scan) that had developed when the APTT was 56.2 s. This patient was also treated with carbasalate-calcium to prevent obstruction in two intracoronary stents, which were utilized after an acute myocardial infarction. Another patient, who had undergone multiple abdominal surgery for severe pancreatitis, died from abdominal hemorrhage within few hours after CAVH/DF and heparin were discontinued, at an APTT of 39.2 s. A third patient died from abundant gastrointestinal hemorrhage as a result of an esophageal perforation of unknown origin. The complication occurred 24 h after the start of CAVH/DF while the APTT was 48.1 s. In ten other patients, administration of heparin was discontinued because of hemorrhagic complications or severe coagulopathy. In all other cases of hemorrhage, the heparin dose was continued, although at a lower rate. Overall, the hemorrhagic complications required on average 2.5 ± 0.1 U of blood (range, 2 to 5).

TABLE 2. Number of filters and types of continuous renal replacement therapies

Type of Filter	CAVH[a] (N = 59)	CAVHDF[b] (N = 181)	Treatment (h)
Acrylonitrile	24%	19%	2280
Polyamide	76%	81%	9480
All	100%	100%	11,760

[a] CAVH, continuous arteriovenous hemofiltration.
[b] CAVHDF, continuous arteriovenous hemodiafiltration.

TABLE 3. Classification, focus, and number of hemorrhagic complications in 78 patients treated with CAVH/DF[a]

Classification	Focus	Number (death)
Major	Intraabdominal	6 (1)
	Along intravascular catheters	18 (-)
	Gastrointestinal	3 (1)
	Oronasopharyngeal	12 (-)
	Intracerebral	1 (1)
Total major		40 (3)
Minor	Macroscopic hematuria	3 (-)
	Epistaxis	3 (-)
	Rectal	1 (-)
	Vaginal	1 (-)
Total minor		8 (-)
All		48 (3)

[a] The definition of hemorrhage was derived from Levine *et al.* (9).

Crude Incidence Rates

The overall incidence of filter coagulation was 13.5 per 1000 h (95% CI, 11.3 to 16.6) in the patients treated with heparin therapy only (APTT 41.7 ± 1.4 s). The occurrence of coagulation gradually decreased from 17.7 ± 2.5 per 1000 h at normal levels of APTT (range, 15 to 35 s) to 9.0 ± 2.7 per 1000 h when the APTT was twofold prolonged (Table 4, test for trend P = 0.031). The overall incidence was 7.6 per 1000 h (95% CI, 5.0 to 11.4) in patients treated with both heparin (APTT 48.5 ± 2.3 s) and coumarin derivatives (INR 3.5 ± 2.4).

Survival time of the filters ranged from 3 to 381 h. There was no difference in filter survival time between treatment with CAVH or CAVHD (Figure 1). Both survival curves lie about a common estimate. Filter survival time, however, was significantly different between the two types of filters (P = 0.003, Figure 2). Mean survival of the filters was 33.8 ± 4.3 h (95% CI,

TABLE 4. Total number and incidence rates of filter-coagulation and patient-hemorrhage dependent on the APTT values in 78 patients treated with CAVH/DF

APTT[a] (s)	CAVH/DF-Time (h)	Filter Coagulation			Patient Hemorrhage		
		Number	Incidence (per 1000 h)	95% CI	Number	Incidence (per 1000 h)	95% CI
Treatment with Heparin Only							
15–35	2718	48	17.7	13.3–23.4	8	2.9	1.5–5.9
35–45	3150	38	12.1	8.8–16.6	7	2.2	1.1–4.7
45–55	1632	21	12.9	8.4–19.7	12	7.4	4.2–12.9
>55	1224	11	9.0[b]	5.0–16.2	9	7.4[c]	3.8–14.1
All (mean, 42)	8724	118	13.5	11.3–16.2	36	4.1	3.0–5.7
Treatment with Coumarin and Heparin							
All (mean, 49)	3036	23	7.6	5.0–11.4	12	4.0	2.2–7.0

[a] APTT, activated partial thromboplastin time (normal values, 15–35 s).
[b] Test for trend over the various strata of APTT, * $P < 0.05$.
[c] Test for trend over the various strata of APTT, ** $P < 0.01$.

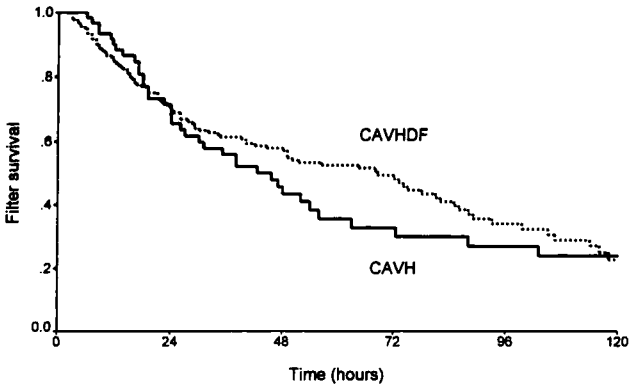

Figure 1. Filter survival time dependent on treatment with continuous arteriovenous hemofiltration (CAVH, $N = 59$) and continuous arteriovenous hemodiafiltration (CAVHDF, $N = 181$). Filter survival time was not statistically significant ($P > 0.2$).

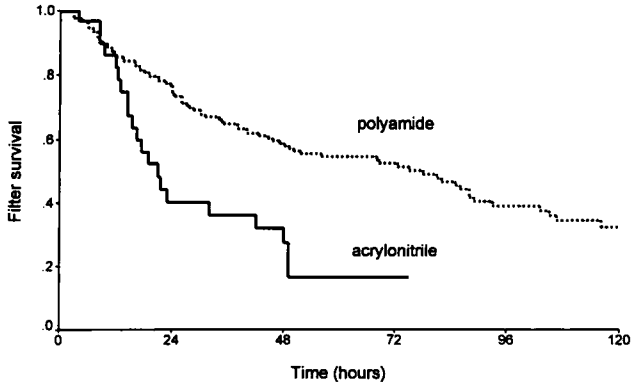

Figure 2. Survival time of Hospal AN69 Multiflow (acrylonitrile, $N = 35$) filters (solid lines) and Gambro FH66 (polyamide, $N = 166$) filters (dotted lines) in patients treated with CAVH/DF. Survival time was significantly different ($P = 0.003$) between the two types of filters.

25.3 to 42.3) in Multiflow AN 69 filters and 104 ± 14.4 h (95% CI, 75.7 to 132.5) in the Gambro FH 66 filters.

The overall incidence of hemorrhage was 4.1 per 1000 h (95% CI, 3.0 to 5.7) in patients treated with heparin only. The incidence of hemorrhage increased approximately threefold from 2.9 ± 1.0 per 1000 h in the normal ranges of the APTT, to 7.4 ± 2.4 per 1000 h when the APTT was twofold prolonged (Table 4, $P = 0.009$). The incidence of hemorrhage during simultaneous use of heparin and coumarin derivatives was 4.0 per 1000 h (95% CI, 2.2 to 7.0). The occurrence of patient hemorrhage was not different for the two types of filters, neither was it influenced by previous clotting in the same treatment period.

Adjusted Estimates

To correct the crude incidence of filter coagulation and patient hemorrhage for the type of filter, mean arterial blood pressure, the transient descents in blood pressure, and platelet count, the data were analyzed in a Cox's proportional hazards model, taking into account that some of these determinants altered over time. In this analysis, the patients on coumarin derivatives were excluded from analysis. There was no heterogeneity between patients in respect to filter survival and the occurrence of patient hemorrhage, as indicated by a goodness of fit test-statistic of $P = 0.15$ and $P = 0.22$ respectively. Therefore, each filter period can be considered as patient-independent observations.

When adjusted for the type of filter, mean arterial blood pressure, decreases in blood pressure, and platelet count, the risk of filter coagulation decreased 25% (hazard rate, 0.77; 95% CI, 0.62 to 0.96) when the APTT increased 10 s (Figure 3). Coagulation of the filters was significantly correlated with transient decreases in blood pressure ($P < 0.001$). In contrast with this pivotal relation between APTT and filter coagulation, no significant correlation was found between the heparin dose and coagulation of the filters. In a similar

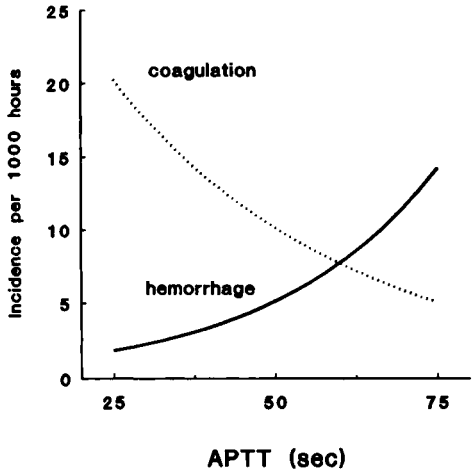

Figure 3. Incidence rates of patient hemorrhage and filter survival time in patients treated with CAVH/DF. Incidence rates were estimated using a Cox's proportional hazards model adjusted for the type of filter, mean arterial blood pressure, decreases in blood pressure, and platelet count.

analysis, the risk for patient hemorrhage increased 50% for every 10-s increase of APTT (hazard rate, 1.50; 95% CI, 1.38 to 1.64). A similar estimate was obtained when the observations were confined to the occurrence of first hemorrhages only, although with a wider confidence interval. The risk for hemorrhage was significantly correlated with the number of platelets ($P < 0.05$). Similar to the occurrence rate of filter coagulation, no significant correlation was observed between the dose of heparin and the occurrence of hemorrhagic complications.

DISCUSSION

In the study presented here, we determined the effect of heparin on filter survival and patient hemorrhage, taking into account several concurrent risk factors. The coagulation of filters was clearly dependent on the APTT values, indicating a beneficial effect of heparin therapy on filter survival. The effect of heparin was stronger after correction for the type of filter, mean arterial blood pressure, decreases in blood pressure, and platelet count. A 25% decrease of filter coagulation was observed for every 10-s increase of APTT.

Remarkably, only the APTT values were correlated with filter survival, whereas the heparin dose was not predictive. This finding corresponds with the literature about the pharmacokinetics and biological effects of heparin: the APTT is variably correlated with the heparin dose (10–15). Besides, the APTT is partly dependent on the level of coagulation factors in association with the critical illness of the patients and dependent on the variable clearance of the prefilter-administrated heparin (8,16,17).

The overall filter survival in our study corresponds roughly with the survival of filters reported in literature (3). Nevertheless, a significant difference of filter-survival was found between the Gambro FH66 (polyamide) filters and the Hospal Multiflow AN69 (acrylonitrile) filters. These findings seem to extend the observation that polyamide membranes are less thrombogenic compared with the acrylonitrile membranes (18). It cannot be excluded, however, that other characteristics of the filters account for the significant difference in performance.

If we take into account the concurrent use of coumarine derivatives, it is remarkable that the overall incidence of filter coagulation decreased almost twofold, without increasing the crude incidence of hemorrhagic complications. This suggest a positive role of coumarin derivatives in filter survival, which has never been described before. It may be possible that contact activation of the intrinsic pathway by the extracorporeal circuit is not the only mechanism of the coagulation of the extracorporeal circuit. Activation of the extrinsic pathway seems to be relevant and is inhibited by coumarin derivatives (19,20).

A similar close relation with the systemic APTT was found for the incidence of hemorrhagic complications. The risk of hemorrhage was increased by 50% for every 10-s increase of APTT. Again, the heparin dose was not correlated with the risk of patient hemorrhage. As expected, the number of platelets was also related with an increase of hemorrhagic complications, whereby thrombocytopenia was thought to be a consequence of the critical illness rather than an unusual side effect of heparin. Three patients died from hemorrhage, although multiple blood transfusions were necessary in all other cases. There was no threshold of the APTT under which hemorrhagic complications did not occur. Apparently, hemorrhages always occur although at higher frequency during heparin treatment.

The prevalence of minor hemorrhages compared with the prevalence of major hemorrhages is strikingly low. Most likely this results from the fact that minor bleeding episodes were of little clinical relevance and therefore underreported. Probably, the occurrence of minor bleeding is incorporated in daily patient care as side effects that are not worth to be mentioned.

In other studies, morbidity and mortality differed widely, depending on the preexisting coagulopathy (4,9,21). This illustrates the difficulty in proposing explicit guidelines for heparin therapy in daily practice. If we use the best risk estimates for the occurrence of filter coagulation and patient hemorrhage, the relation with the APTT could be presented as in Figure 3. It illustrates that in our study, the incidence of hemorrhage and of filter coagulation becomes equal at an APTT of 58 s, an apparent optimal value. As the consequence of filter coagulation is predominantly financial, whereas the consequence of hemorrhage could be lethal, it seems justifiable to titrate heparin therapy in a safer range of APTT values: 35 to 45 s (1.5 to 2 times normal). Again, it must be realized that there is no "threshold-APTT" below which heparin is

safe. Two of the three fatal hemorrhages observed occurred at APTT values below 50 s.

Until now, heparin has been the most frequently used anticoagulant to prevent the extracorporeal circuit from coagulation (19). The associated complications have initiated a search for alternative methods of anticoagulation, such as low-dose heparin (5), prostacyclin (22,23), or trisodium-citrate (3,4). The interpretation of these studies is hampered by the fact that the patients with the most serious coagulation disorders were anticoagulated with the alternative methods. To our knowledge, a randomized controlled study, comparing heparin with other forms of anticoagulation, has not been performed yet.

In conclusion, we propose the use of systemic APTT as a predictive parameter for filter survival and patient hemorrhage during heparin therapy. Efficacy and safety of heparin therapy seems optimal at an APTT between 35 and 45 s. The intensity of the anticoagulation is dependent on general cost-benefit considerations and individual patient characteristics.

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