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Anti-PF4/Heparin antibodies associated with repeated hemofiltration-filter clotting: a retrospective study

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Abstract

Introduction: Heparin-induced thrombocytopenia is an immune mediated adverse drug reaction that is associated with a procoagulant state and both arterial and venous thrombosis. After observing two cases of repeated hemofiltration-filter clotting associated with high anti-PF4/Heparin antibody concentrations, we systematically measured anti-PF4/Heparin antibody concentration in all cases of unexpected and repeated hemofiltration-filter clotting during continuous veno-venous hemofiltration (CVVH). The aim of this study was to identify factors associated with positive anti-PF4/Heparin antibody in the case of repeated hemofiltration filter clotting.

Methods: We reviewed the charts of all patients who had an anti-PF4/Heparin antibody assay performed for repeated hemofiltration filter clotting between November 2004 and May 2006 in our surgical intensive care unit. We used an enzyme-linked immunoabsorbent assay (ELISA, HPIA, Diagnostica Stago, Paris, France) with an optical density (OD)>1 IU considered positive.

Results: During the study period, anti-PF4/Heparin antibody assay was performed in 28 out of 87 patients receiving CVVH. Seven patients were positive for anti-PF4/Heparin antibodies (OD 2.00[1.36-2.22] IU) and 21 were antibody-negative (OD 0.20[0.10-0.32] IU). Baseline characteristics, platelet counts, aPTT ratios were not different between the two groups. CVVH duration was significantly decreased in antibody-positive patients (5.0[2.5-7.5] vs 12.0[7.5-15 24.0] hours, p=0.007) as was CVVH efficiency (urea reduction ratio: 17[10-37] vs 44[30-52]%, p=0.04) on heparin infusion. Anti-PF4/Heparin antibody concentration was inversely correlated with CVVH duration. The ROC curve showed that a 6-hour cut-off was the best CVVH session duration to predict a positive antibody test (sensitivity: 71%, specificity: 85%, area under the curve: 0.83). CVVH

duration (32[22-37] hours, $p<0.05$) and urea reduction (55[36-68]%, $p<0.03$) were restored by danaparoid sodium infusion.

Conclusions: Repeated hemofiltration-filter clotting in less than 6 hours was often associated with the presence of anti-PF4/Heparin antibodies, regardless of the platelet count. In antibody-positive patients, replacement of heparin by danaparoid sodium allowed restoration of CVVH duration and efficiency.

Introduction

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated adverse effect of heparin. The initial description concerned arterial thrombosis during unfractionated heparin (UFH) therapy [1]. HIT has subsequently been associated with an increased risk of venous or arterial thrombosis [2-4]. The pathophysiology of HIT consists of generation of anti-PF4/Heparin antibodies, resulting in platelet and endothelial cell activation, leading to a procoagulant state [5].

Continuous veno-venous hemofiltration (CVVH) is widely used for renal replacement. Because UFH is often used as anticoagulation therapy, patients undergoing CVVH might be at risk of anti-PF4/Heparin antibody generation or HIT. One clinical feature of HIT in this context could be repeated hemofiltration-filter clotting [6, 7]. In our surgical intensive care unit (ICU), we recently observed two cases of HIT responsible for repeated hemofiltration-filter clotting in the absence of typical thrombocytopenia [8] and we then systematically measured plasma anti-PF4/Heparin antibody concentration in all patients with repeated hemofiltration-filter clotting during CVVH, with no obvious cause. The purpose of this study was to report a series of patients in whom an anti-PF4/Heparin antibody test was performed and to identify factors associated with a positive test in this particular setting, in order to precise when one should perform the test.

Patients and methods

Patients

Between November 1st 2004 and May 1st 2006, 87 patients underwent CVVH. Twenty eight of these patients experienced repeated (≥2) hemofiltration-filter clotting before the scheduled end of the CVVH session (24 to 48 hours) with no obvious cause and anti-PF4/Heparin antibodies were assayed. We reviewed the charts of these 28 patients. Because of the retrospective nature of the study, no written consent was requested in accordance with French law. The study was approved by our IRB. For each patient, general characteristics, platelet counts at various time-points (admission, nadir (lowest reported concentration), day of anti-PF4/Heparin antibody assay and maximal count), CVVH session duration and efficiency (assessed by the urea reduction ratio before/after each session) were recorded. The duration of CVVH sessions was obtained from the CVVH surveillance sheet, on which nurses recorded data hourly routinely.

For each patient, an objective clinical probability scoring system was used to calculate the likelihood of heparin-induced thrombocytopenia according to the Four T-Score [9]. For this purpose, we attributed 1 point for the third item, “Thrombosis”, considering that the hemofiltration filter clotting was equivalent to a “recurrent thrombosis”.

CVVH settings

CVVH was performed using the Aquarius system (Aquarius, Edwards Lifesciences, Switzerland). Blood flow was set at 250-300 ml/min; ultrafiltrate flow at 35 ml/kg/h and substitution solutions (Hemosol® or Prismasol® from Hospal, France) were delivered 1/3 pre-filter and 2/3 post-filter.

A dual-lumen 11.5F catheter (Mahurkar™, Tyco healthcare, Switzerland) was used, inserted into either the femoral or right internal jugular veins. Catheters were changed in

all patients at least once before anti-PF4/Heparin antibody assay, to exclude catheter dysfunction.

Anticoagulation management

Before starting the CVVH session, the hemofiltration circuit was heparinized by priming with 10,000 IU of UFH (Héparine Choay®, Sanofi-Synthelabo, France) in 2,000 ml of saline solution. UFH was then continuously infused in the hemofiltration circuit to obtain an activated partial thromboplastin time (aPTT) ratio ranging between 1.2 and 2. The APTT ratios were measured systematically, from the arterial line.

In the case of positive PF4 test, UFH was replaced by danaparoid sodium (Orgaran®, ORGANON SA, Eragny-sur-Epte, France) using the manufacturer's recommendations to obtain a specific danaparoid anti-Xa activity between 0.4 and 0.6 IU/ml.

PF4 test and heparin-induced platelet activation assay

Anti-PF4/Heparin antibodies were measured by enzyme-linked immunoabsorbent assay (ELISA, HPIA, Diagnostica Stago, Paris, France) according to the manufacturer's recommendations. The anti-PF4/Heparin antibody was considered positive (PF4+) when optical densities (OD) were greater than 1 IU. For anti-PF4/Heparin antibody- positive patients, a Platelet-Rich-Plasma (PRP) aggregation assay was performed. Briefly, a plasma sample was incubated with donor platelet-rich plasma and therapeutic (0.5 to 1 IU/ml) or high (100 IU/ml) UFH concentration in an aggregometer (Chronolog 490, Kordia Life Sciences, Netherlands) at 37°C. Platelet aggregation was monitored for 20 minutes. Results were considered positive if aggregation was ≥ 20% with therapeutic

UFH concentration and absent with high UFH concentration. Appropriate positive and negative controls (stored patient plasma) were run in parallel with plasma samples. Cross-reactivity with danaparoid sodium was also recorded under the same conditions.

Statistical analysis

Data are presented as medians [interquartile range] and compared with a Mann-Whitney or a Chi-square test. Patients were classified into two groups (PF4+ and PF4-) according to anti-PF4/Heparin antibody concentration. For PF4+ patients, duration and efficiency of CVVH sessions under UFH and danaparoid were compared with a Wilcoxon rank test. A Receiver Operating Characteristic (ROC) Curve was used to determine the best cut-off value for CVVH duration to predict a PF4+ test. All statistics were performed with the MedCalc® software (MedCalc Software, Belgium). $p<0.05$ was considered significant.

Results

Patients' characteristics

Among the 28 patients with unexplained hemofiltration-filter clotting, seven were anti-PF4/Heparin -antibody-positive. Baseline characteristics were not different between the two groups (PF4 + or -), except for a higher SAPS II for PF4- patients (Table 1). None of the patients had a four T-score of less than 4, indicating that they all had an intermediate or high pre-test probability of HIT. A 4T score of at least 7 had a positive predictive value of 100% and a negative one of 84% fro the diagnosis of HIT, with a sensitivity of 43%. Four of the 7 PF4+ patients (Table 1 No. 1-4) also had a positive PRP aggregation assay, and may be considered as having a very likely diagnosis of HIT [2, 6].

Among the seven patients with HIT, two also had a vascular thrombosis, leading to the diagnosis of HITTS: one had an ischemic stroke (n° 4) and the other one a pulmonary embolism (N°5).

Platelet counts

The platelet count and platelet count variations did not differ between the two groups at any time-point (Tables 1 and 2). In four patients (1 PF4+ and 3 PF4-), the platelet count was higher than 100.10^9/L the day of anti-PF4/Heparin antibody test (Table 1).

CVVH sessions

Main CVVH session characteristics are summarized in tables 1 and 2. No significant difference was observed in terms of aPTT ratios, regardless of the value considered.
The duration of CVVH sessions was significantly decreased in PF4+ patients (Table 1, p=0.007). An inverse correlation was observed between the anti-PF4/Heparin antibody concentration (OD) and the duration of CVVH sessions (r^2=0.24, p=0.01).
As CVVH session duration was the only parameter associated with positive antibodies, we assessed the most relevant duration to predict a positive test. The ROC curve analysis showed that 6 hours was the best cut-off to predict a positive anti-PF4/Heparin antibody test (with a sensitivity of 71%, a specificity of 85% and an area under the curve of 0.83)(Figure 1).
The efficiency of CVVH sessions (assessed by the urea reduction ratio) was also decreased in PF4+ patients (Figure 2). The use of danaparoid sodium as replacement for UFH allowed restoration of adequate CVVH duration (32[22-37] hours, p<0.05) and efficiency (urea reduction: 55[36-68] %, p<0.03) for PF4+ patients (Figure 2).

Discussion

Repeated hemofiltration-filter clotting leading to anti-PF4/Heparin antibody assay is frequent in our experience. We report a large proportion of patients with positive anti-PF4/Heparin antibodies (7 out of 28). A CVVH session lasting less than 6 hours was associated with positive antibodies.

As the aim of this study was not to assess the prevalence of HIT or positive anti-PF4/Heparin antibodies in our overall ICU population, we did not measure anti-PF4/Heparin antibody for patients without hemofiltration-filter clotting. However, it is unlikely that “unselected” patients would have a high rate of anti-PF4/Heparin positive-antibodies. Indeed, the incidence of HIT in intensive care patients is about 1% [6, 10]. Furthermore, there are no data in the literature to support routine anti-PF4/Heparin antibody assays without a clinical suspicion of HIT or thrombosis/clotting on heparin therapy [2, 6].

We and others have already described cases of repeated hemofiltration-filter clotting associated with positive anti-PF4/Heparin antibodies [7, 8]. However, such a large proportion of patients with positive anti-PF4/Heparin antibodies was not expected and has not been previously reported. In their large cohort of 2,046 postoperative critically ill patients, Gettings et al reported only 19 (0.9%) patients with anti-PF4/Heparin positive antibodies [10]. The presence of positive antibodies may be an independent risk factor for thrombotic events, apart from the diagnosis of HIT [11], as anti-PF4/Heparin

antibodies are associated with dose-dependent activation of coagulation [12]. We therefore decided to use a high cut-off value for positive antibodies OD (>1 IU). It should be emphasized that the anti-PF4/Heparin antibody OD observed in our patients was inversely correlated with the CVVH session duration. The time to onset of hemofiltration-filter clotting appeared to be shorter in patients with higher anti-PF4/Heparin antibody titer, possibly indicating more intense activation of coagulation.

Despite the high cut-off chosen to define positive antibodies, a large number of patients presented positive antibodies. This is probably related to our study population, as the probability of HIT (or positive anti-PF4/Heparin antibodies) depends on the population studied [2, 9, 13]. In our study, patients were highly selected and represented less than one third of all patients undergoing CVVH in our unit. Furthermore, complicated cardiac surgery patients account for the majority of our case mix and, together with orthopedic patients, are known to present the highest risk of anti-PF4/Heparin positive-antibodies [2, 14, 15].

We do not assume that all 7 anti-PF4/Heparin antibody-positive patients had true HIT, but the diagnosis of HIT was very likely in 4 of these 7 patients and was probable in the remaining 3 patients according to published criteria [6]. Furthermore, a strong positive test result (OD>1) is associated with a high likelihood ratio for HIT [2]. The diagnosis of HIT is based on two aspects: clinical features, including the course of platelet count (with a >50% fall over a typical time-scale [16]) and laboratory features, including confirmation tests [2, 17]. In our study population, the timing of HIT suspicion was within the usual range. Moreover the Four T-scores [9], although not validated for ICU patients,

indicated an at least intermediate risk for all patients. Although thrombocytopenia is the most common feature of HIT, it is also a very common finding in ICU patients and could be related to many causes, including CVVH itself. In fact, platelet counts were low in both groups (PF4+ and PF4-). The time to clotting of the hemofiltration-filter therefore appeared to be the only factor associated with positive anti-PF4/Heparin antibodies. Interestingly, the six-hour cut-off reported here is consistent with the 7.5-hour interval before clotting observed by Samuelsson et al [7].

Finally, although the diagnosis of HIT was not certain for all anti-PF4/Heparin antibody-positive patients, replacement of UFH by danaparoid sodium allowed restoration of CVVH duration and efficiency, supporting the clinical relevance of anti-PF4/Heparin antibody assay in the case of repeated hemofiltration-filter clotting, at least in a surgical ICU patient population. Interestingly, the duration of CVVH sessions under danaparoid sodium we observed were closed to the ones described by de Pont et al [18]. In accordance with the later authors, we did not observed any bleeding complications during danaparoid therapy. Furthermore, once the diagnosis of HIT is considered, all heparin exposure should cease, including intravenous catheter locks.

Because of the retrospective nature of the study, we are not able to precise the causes of hemofiltration filter clotting in the remaining 21 patients with negative anti-PF4/Heparin antibody. In particular we did not perform PRP aggregation assays or serotonin release assay to search for HIT with antigenic target different from PF4, nor did we assess the anti-thrombin III levels of these patients, but they had elevated aPTT ratios indicating a certain activity of UFH. Further studies focusing on hemofiltration filter clotting are needed to better describe this issue and the different factors associated with

filter clotting (such as coagulation activation or abnormalities, as well as CVVH settings or catheter dysfunction).

Conclusion

We report a large proportion of anti-PF4/Heparin antibody-positive patients in the case of repeated hemofiltration-filter clotting during CVVH, particularly when clotting occurred in less than 6 hours. In these cases, replacement of UFH by danaparoid sodium (or other agents such as citrate or saline flushes) may be useful.

Key Messages

- HIT diagnosis and positive anti-PF4/Heparin antibody was frequently observed in case of repeated hemofiltration filter clotting during CVVH under heparin.
- Hemofiltration filter clotting in less than 6 hours was the best predictor of positive anti-PF4/Heparin antibody; while platelet count and its variation, was not associated with positive test.
- The replacement of heparin by danaparoid sodium allowed the restoration of CVVH duration and efficiency, in anti-PF4/Heparin antibody-positive patients.

Abbreviations

HIT = heparin-induced thrombocytopenia

UFH = unfractionated heparin

CVVH = continuous veno-venous hemofiltration

ICU = intensive care unit

APTT = activated partial thromboplastin time

OD = optical densities

PRP = Platelet-Rich-Plasma

PF4 + (or -) = anti-PF4/Heparin antibody-positive (or negative)

ROC = Receiver Operating Characteristic

Competing Interests

For each author listed on this manuscript there is no personal or financial support or author involvement with organization with financial interest in the subject matter and no conflict of interest exists. The authors declare that they have no competing interests.

Authors' contributions

SL and PP designed the study. SL, PP, AG, AB, PM treated the patients. SL, PP, AG, AB reviewed the charts of the patients. NA was responsible for the laboratory assays. SL was responsible for the analysis of the data.

All authors contributed in the writing and critical appraisal of the manuscript.

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Figure legends

Figure 1 : Receiver-operator characteristic curve for CVVH duration

ROC curve used to assess the best cut-off for time to hemofiltration-filter clotting to predict a positive PF4 test. Arrow showing that a 6-hour duration of CVVH session is the most accurate cut-off (sensitivity: 71%, specificity: 85%, area under the curve: 0.83).

Figure 2: Duration and efficiency of CVVH sessions.

Boxes represent medians, interquartile ranges and 10^{th} 90^{th} percentiles of mean duration of CVVH sessions (upper panel) and urea reduction ratios ([(urea before-urea after)/urea before]x100, lower panel) observed in PF4+ (n=7) and PF4- (n=21) patients when using unfractionated heparin (50 and 132 sessions for PF4+ and PF4- patients, respectively) and in PF4+ patients when using danaparoid sodium for anticoagulation (17 sessions). * $p<0.05$ compared to PF4+ (using a Mann-Whitney test), # $p=0.027$ compared to PF4+ (using a Wilcoxon rank test). There was no difference between PF4- and danaparoid CVVH durations ($p=0.17$) or urea reduction ($p=0.27$).

Table 1: Characteristics of the study population.

	No.	Gender	Age (yrs)	SAPS II	SOFA	Type of Surgery	Sepsis	Shock	MV	Time to onset (days)			ICU length of stay (days)	Platelet counts (10^9/L)		Score 4Ts	aPTT ratios		CVVH Duration (hours)	PF4 (OD)	Death
										ICU	CVVH	UFH		D_0	D_{PF4}		mean	≥1.2 (%)			
PF4+	1	M	54	34	12	Cardiac	N	Y	Y	8	6	8	22	42	10	5	1.2	50	14	1.18	N
	2	M	59	29	6	Cardiac	N	N	N	6	6	9	13	76	51	7	1.2	100	2	2.26	N
	3	M	63	50	13	Cardiac	Y	Y	Y	9	8	9	28	101	20	7	1.3	33	4	2.68	N
	4	F	49	44	11	Cardiac	N	Y	Y	7	7	8	8	251	95	7	1.2	33	6	1.89	Y
	5	M	62	86	16	Trauma	Y	Y	Y	15	13	14	22	163	66	5	2.4	100	5	1.18	Y
	6	M	55	52	12	Cardiac	N	Y	Y	10	8	11	26	144	200	4	1.9	100	2	2.00	N
	7	M	57	42	14	Cardiac	Y	Y	Y	16	15	20	43	78	46	5	2.6	100	8	2.11	N
Total		6M	57	44 *	12.5	6 cardiac	3	6	6	9	8	9	22	101	51	5	1.3	100	5 *	2.00 *	2
(n=7)		(86%)	[55-62]	[36-51]	[12-14]	(86%)	(43%)	(86%)	(86%)	[8-15]	[6-13]	[9-14]	[18-28]	[77-158]	[26-88]	[5-7]	[1.2-2.4]	[50-100]	[2.5-7.5]	[1.36-2.22]	(40%)
PF4-	8	F	78	64	11	Visceral	Y	Y	Y	4	2	5	4	109	48	6	3.1	100	19	0.11	Y
	9	M	51	51	8	Visceral	Y	Y	Y	5	5	5	16	413	234	6	1.6	75	4	0.19	N
	10	M	58	65	19	Cardiac	Y	Y	Y	3	2	10	26	214	42	6	1.2	67	10	0.40	N
	11	M	77	68	15	Cardiac	Y	Y	Y	14	14	24	47	176	52	5	1.8	100	12	0.13	Y
	12	M	78	56	16	Cardiac	N	Y	Y	4	4	5	15	100	22	5	1.7	100	12	0.26	Y
	13	M	83	89	18	Cardiac	Y	Y	Y	4	3	5	28	86	33	6	1.8	100	9	0.17	Y
	14	M	78	59	11	Cardiac	Y	Y	Y	5	2	4	14	141	31	6	1.8	100	10	0.07	Y
	15	M	37	35	14	Trauma	Y	Y	Y	9	7	7	25	146	63	4	1.1	25	7	0.09	N
	16	F	73	62	15	Cardiac	Y	Y	Y	36	36	39	50	94	48	5	3.9	100	24	0.29	Y
	17	M	79	59	10	Visceral	Y	Y	Y	9	9	9	12	169	86	6	1.4	100	31	0.18	Y
	18	M	60	49	10	Cardiac	N	N	Y	5	3	5	14	60	39	5	1.3	100	24	0.09	N
	19	M	48	48	8	Visceral	Y	Y	Y	6	2	9	27	258	167	6	1.8	100	24	0.08	Y
	20	F	75	54	11	Visceral	Y	Y	Y	6	4	7	12	86	21	6	1.9	100	4	0.34	Y
	21	M	60	39	13	Cardiac	N	Y	Y	4	3	5	58	61	47	6	1.5	100	24	0.19	N
	22	M	75	56	13	Cardiac	Y	Y	Y	19	17	20	37	105	45	5	1.2	25	8	0.83	Y
	23	M	78	57	13	Cardiac	Y	Y	Y	5	4	6	61	67	44	6	1.0	0	13	0.02	N
	24	M	64	73	14	Visceral	N	Y	Y	16	16	16	26	206	95	6	1.4	100	16	0.24	N
	25	M	38	71	20	Vascular	Y	Y	Y	4	4	4	33	210	49	6	1.7	100	18	0.20	N
	26	M	69	66	13	Cardiac	Y	Y	Y	5	4	5	11	140	48	6	1.1	25	6	0.51	Y
	27	F	37	52	13	Cardiac	Y	Y	Y	6	5	9	27	57	234	6	1.4	100	7	0.58	N
	28	M	75	44	10	Visceral	Y	Y	Y	22	20	24	53	203	42	5	1.4	86	24	0.29	Y
Total		17 M	73	57	13	12 cardiac	17	20	21	5	4	7	26	140	48	6	1.5	100	12	0.20	12
n=21)		(81%)	[56-78]	[50-65]	[10-15]	(57%)	(81%)	(95%)	(100%)	[4-9]	[3-10]	[5-12]	[14-39]	[86-204]	[41-69]	[5-6]	[1.3-1.8]	[73-100]	[7.5-24]	[0.10-0.32]	(57%)

Patients were classified into 2 groups (PF4+ and PF4-) according to anti-PF4/Heparin antibody concentration (optical densities, OD, >1 IU or not). PF4+ patients 1 to 4 also had a positive functional test for heparin-induced thrombocytopenia (PRP aggregation test). No differences were observed between these four patients and the remaining three patients with a negative functional test. The type of surgery for the two trauma patients was orthopedic and visceral for patient No. 5 and visceral surgery only for patient No. 15.

Gender: M, male; F, female. SAPS II: simplified acute physiologic score [19]. SOFA: Sepsis-related organ failure assessment score [20]. Y, yes; N, no. Shock was defined as need for Vasopressor support. MV, mechanical ventilation. Time to onset is the time between intensive care unit (ICU) admission, or continuous veno-venous hemofiltration (CVVH), or unfractionated heparin (UFH) and the day of anti-PF4/Heparin antibody assay. D_0, day of admission; D_{PF4} day of anti-PF4/Heparin antibody assay. The 4Ts score was calculated by considering that hemofiltration-filter clotting did constitute a “recurrent thrombosis” (= 1 point)[9]. aPTT: activated partial thromboplastin time observed during the CVVH session with hemofiltration-filter clotting. Results are expressed as medians [Q1-Q3] or numbers. * $p<0.05$.

Table 2: Laboratory and CVVH parameters.

	PF4+ (n=7)	PF4- (n=21)	*p*
Creatinine before first CVVH (µmol/L)	600[247-742]	403[312-441]	*0.34*
Urea before first CVVH (mmol/L)	17[10-25]	15[12-24]	*0.91*
Number of CVVH sessions	5[4-11]	5[3-9]	*0.65*
Mean CVVH duration* (hours)	10.4[9.6-18-4]	22.7[15.7-22.3]	***0.03***
Mean urea reduction ratios* (%)	17[10-37]	44[30-52]	***0.04***
Platelet nadir (10^9/L)	40[24-46]	35[17-43]	*0.54*
Maximum platelet count (10^9/L)	324[238-366]	286[182-403]	*0.81*
PF4 platelet count variation (D_0-D_{PF4}) (%)	59[35-73]	56[35-73]	*0.98*
Maximum platelet count variation (D_0-D_{nadir}) (%)	77[49-81]	79[55-87]	*0.81*
Mean minimum aPTT ratios¥	1.20[1.12-1.22]	1.35[1.10-1.56]	*0.35*
Mean maximum aPTT ratios¥	1.85[1.65-2.12]	2.19[1.51-2.93]	*0.35*

Platelet count variations were calculated as follows: [(platelet D_0-platelet D_x) / platelet D0]x100; where platelet D_0 is the platelet count on admission and platelet D_x is the platelet count on the day of anti-PF4/Heparin antibody assay (for D_{PF4}) or the minimal platelet count (for D_{nadir}). aPTT: activated partial thromboplastin time on heparin therapy during all CVVH sessions. Results are expressed as medians [Q1-Q3]. * for PF4+ patients, mean duration and efficiency of CVVH sessions before replacement of unfractionated heparin by danaparoid. ¥ means of minimum and maximum aPTT ratios observed during all the CVVH sessions before D_{PF4}.
CVVH: continuous veno-venous hemofiltration
aPTT: activated partial thromboplastin time

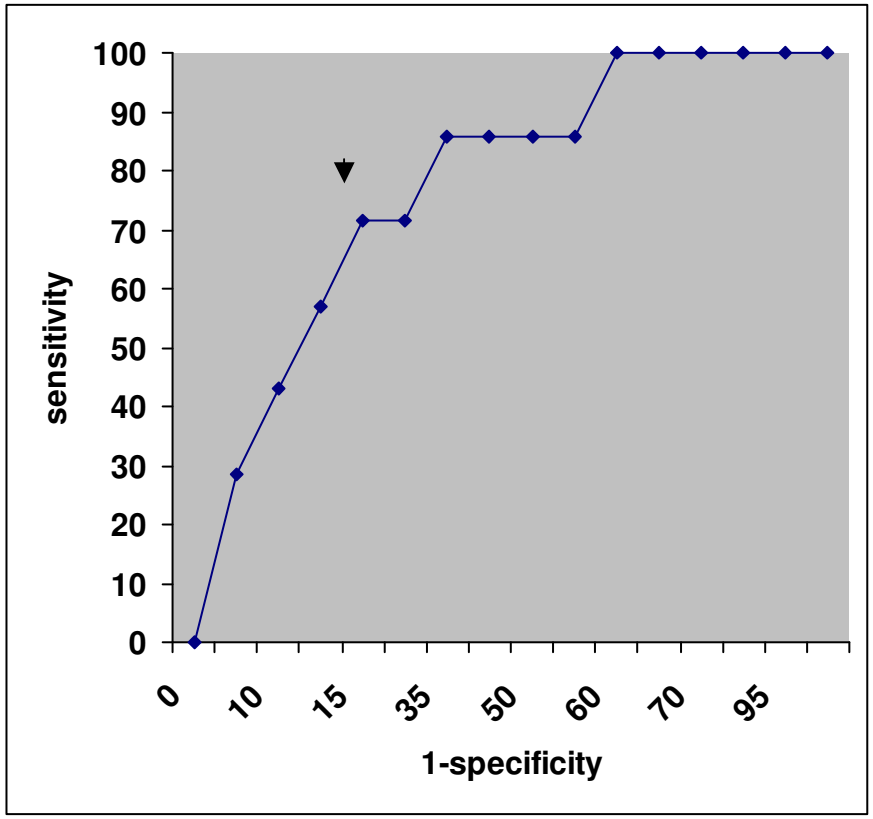
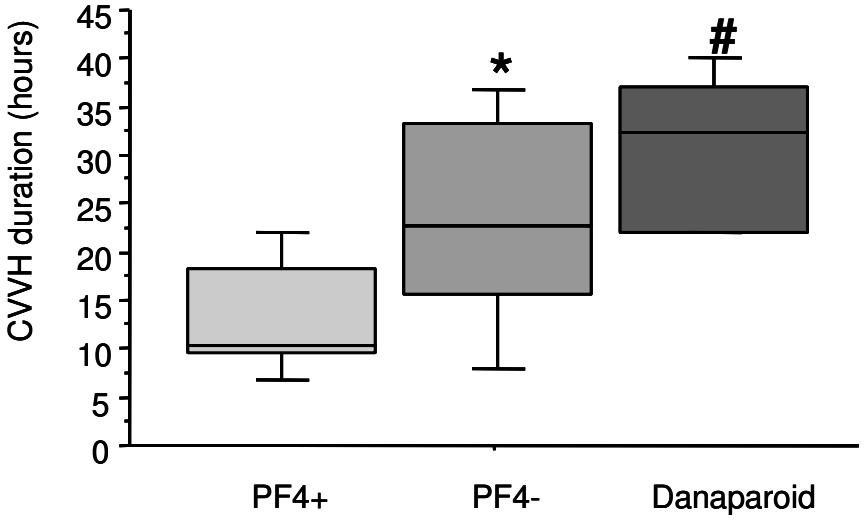

100
90
80
70
60
50
40
30
20
10
0
sensitivity
0
10
15
35
50
60
70
95
1-specificity

Figure 1


CVVH duration (hours)
45
40
35
30
25
20
15
10
5
0
*
#
PF4+
PF4-
Danaparoid

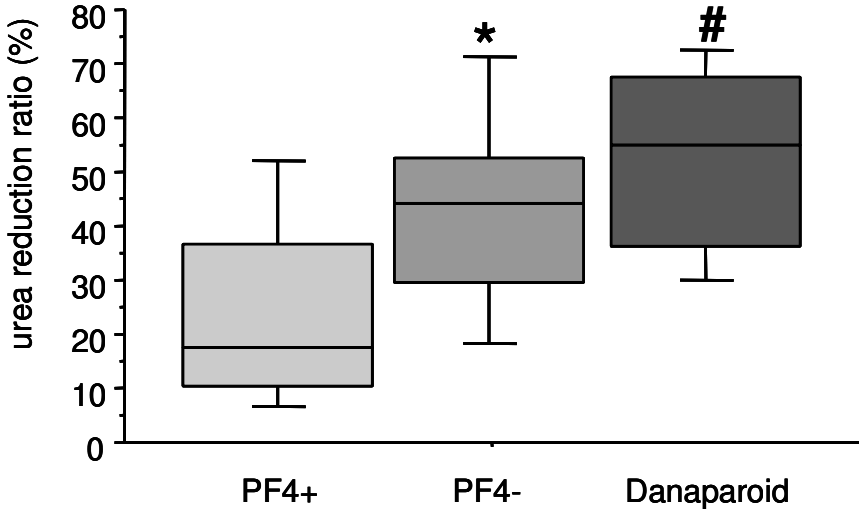

urea reduction ratio (%)
80
70
60
50
40
30
20
10
0
*
#
PF4+
PF4-
Danaparoid

Figure 2