Hemodialysis Does Not Induce Detectable Activation of the Contact System of Coagulation

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Introduction: Systemic anticoagulation is administered during hemodialysis to prevent clotting of the extracorporeal circuit. The role of contact system activation in thrombin generation during hemodialysis using current era dialyzer membranes is unknown.

Methods: We performed a single-center randomized crossover study. Ten patients treated with hemodialysis underwent 3 standardized hemodialysis sessions. For every patient, each session was performed with a different type of dialyzer membrane (polyphenylene [PP], polymethylmetacrylate [PMMA], polyethylenimine-coated polyacrylonitrile [AN69ST]). Blood samples were collected before and 5, 15, 30, 90, and 240 minutes after blood pump start to evaluate coagulation activation (thrombin–antithrombin complex [TAT], prothrombin fragment 1+2 [PF1+2], activated factor XII [FXIIa], kallikrein, activated factor XI [FXIa]). Plasma of healthy volunteers ($n = 20$) was used as a reference.

Results: Baseline TAT and PF1+2 levels were higher in hemodialysis patients compared to healthy controls (median [interquartile range] for TAT: 3.3 [2.9–4.2] vs. 2.4 [2.3–2.5] μg/l [$P = 0.0002$] and for PF1+2: 647 [478–737] vs. 138 [125–254] pmol/l [$P < 0.0002$]). Despite the use of systemic anticoagulation, TAT further increased during treatment, with the increase starting after 30 minutes (median TAT at t240: 9.0 μg/l (PP), 5.5 μg/l (PMMA), and 7.2 μg/l (AN69ST), all $P < 0.05$ vs. baseline). Contact system markers FXIIa and kallikrein did not differ significantly between dialysis patients and healthy controls, whereas baseline FXIa levels were significantly lower in dialysis patients compared to healthy controls ($P = 0.001$). Levels of all contact system markers remained unchanged during hemodialysis with all types of dialyzer membranes.

Conclusion: Routine hemodialysis using systemic heparin anticoagulation induces coagulation activation without measurable contact system activation.

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Platelets, leukocytes, and the coagulation cascade are activated during hemodialysis.[1–7] In clinical practice, systemic anticoagulation is used to prevent clotting of the extracorporeal circuit during hemodialysis,[8] which can lead to significant blood loss if clotting prevents blood retransfusion from the dialysis circuit. If blood clotting is limited to dialyzer fibers without impairing blood flow in the extracorporeal circuit, effective dialyzer surface area is reduced, impairing treatment efficacy. Thrombin generation markers thrombin–antithrombin complex (TAT) and prothrombin fragment 1+2 (PF1+2) (Figure 1) are increased after dialysis, despite systemic anticoagulation.[3] Thrombin generation and clotting result from activation of the coagulation cascade. Two coagulation pathways have been defined: the extrinsic or tissue factor pathway, and the intrinsic or contact system pathway, with interconnections between the 2 pathways at several levels (Figure 1). The contact system pathway of coagulation is initiated when FXIIa cleaves factor XI (FXI) to generate FXIa. FXIIa

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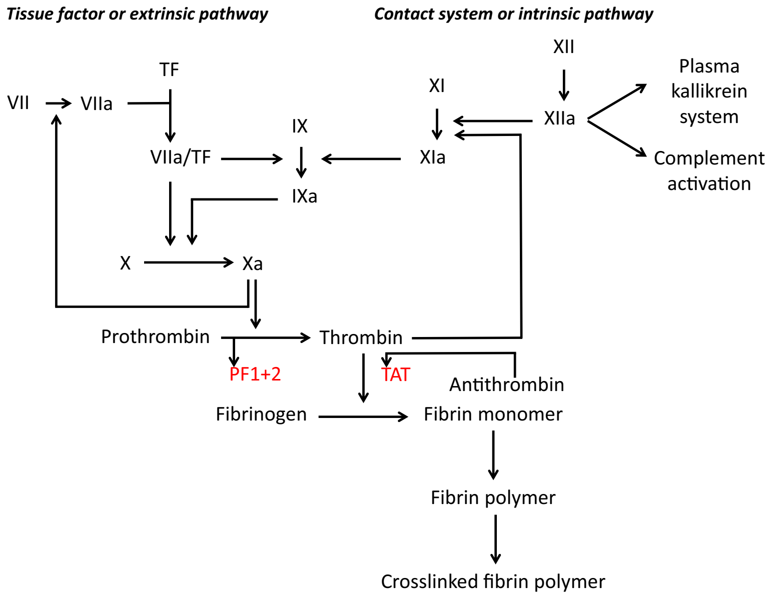

Figure 1. Concise overview of the coagulation cascade, including the tissue factor (TF) pathway and the contact system pathway. Thrombin generation markers prothrombin fragment 1+2 (PF1+2) and thrombin–antithrombin complex (TAT) are denoted in red. PF1+2 is a split product when prothrombin is converted into thrombin. Antithrombin binds thrombin and forms the thrombin–antithrombin complex.

results from contact of blood with negatively charged surfaces, which induces conformational changes of factor XII (FXII). Besides initiation of coagulation, FXIIa also activates the proinflammatory kallikrein–kinin system and the classical complement pathway.[9]

Historical clinical reports and *in vitro* experiments suggest that the contact system of coagulation is activated during hemodialysis. Anaphylactoid reactions observed during hemodialysis using AN69 membranes have been attributed to bradykinin accumulation secondary to kallikrein activation.[10,11]

In the past 2 decades, improvements have been made to the biocompatibility of dialyzer membranes, resulting in lower complement activation by modern membranes.[12] Nevertheless, anticoagulation remains necessary to prevent extracorporeal circuit clotting.[13] The role of contact system activation in thrombin generation induced by current generation dialyzer membranes is unknown.

From a therapeutic perspective, novel anticoagulants targeting FXI and FXII have been developed and studied recently.[14–17] These novel drugs exert the additional advantage of inducing an antithrombotic effect without affecting normal hemostasis.[15]

The question arises of whether these drugs could target hemodialysis-induced coagulation activation and inflammation. The aim of the current study was to evaluate contact system activation and overall coagulation activation during *in vivo* hemodialysis in prevalent hemodialysis patients, using current generation dialyzer membranes. A crossover study design allowed assessment of differences among regular dialyzer membranes.

METHODS

Study Population and Study Design

We performed a single-center randomized crossover study. Ten patients older than 18 years and treated with maintenance hemodialysis (>3 months) underwent 3 hemodialysis study sessions. All patients were treated with 80 to 100 mg acetylsalicylic acid daily and dialyzed at Universitair Ziekenhuis Brussel. Exclusion criteria were clopidogrel or anticoagulant therapy, active infection, presence of central venous catheter or arteriovenous graft, and known vascular access dysfunction. Each of the 3 hemodialysis study sessions per patient was performed with a different type of dialyzer membrane (polyphenylene [PP; Phylter 1.6, Medtronic Belgium, Brussels, Belgium], polymethylmetacrylate [PMMA; BKU 1.6, Toray Industries, Tokyo, Japan], polyethylenimine-coated polyacrylonitrile [AN69ST; Evodial 1.65, Baxter Belgium, Eigenbrakel, Belgium]). Before study start, 18 sealed opaque envelopes were prepared, each containing a specific membrane order (each possible order used 3 times). After successful screening, 1 envelope was blindly picked for each patient, and the assigned membrane order was transcribed onto the patient's study chart by the principal investigator (KF).

All patients were dialyzed through an arteriovenous fistula of the upper limb using Nipro Dialysis Cath 14G catheter needles (Nipro Europe N.V., Mechelen, Belgium). Patients received a bolus of 20 IU/kg unfractionated heparin (UFH) at treatment start, and a maintenance dose of 15 IU/kg per hour UFH during the first 3 hours of the hemodialysis session. Treatment sessions were standardized as to duration (4 hours), priming procedure, dialyzer monitor (DBB-EXA, Nikkiso, Tokyo, Japan), blood and dialysate flow rates (350 ml/min and 700 ml/min, respectively), and dialysate temperature (36 °C). During study treatments, the extracorporeal blood circuit was not used for i.v. medicine administration.

Twenty healthy controls served as the reference population. Written informed consent was obtained from each subject, and the hospital's medical ethics committee granted full ethical approval. The study was registered under CT.gov NCT03090984.

Biological Analyses

Blood samples were taken through the arteriovenous fistula used for dialysis access and collected before dialysis start and before the UFH bolus (t0), and 5 (t5), 15 (t15), 30 (t30), 90 (t90), and 240 (t240) minutes after dialysis start. In healthy controls (n = 20), a single venipuncture was performed. Blood was collected into 3.2% citrate blood collection tubes, centrifuged at 1500 g at room temperature for 10 minutes, followed by storage of the plasma at −70 °C. Blood samples served to evaluate coagulation activation (TAT, PF1+2), and more specifically, activation of the contact system (FXIIa, kallikrein, FXIa).

Assay Methods

Commercial enzyme-linked immunosorbent assays (ELISAs) were used for the measurement of TAT (Enzygnost TAT micro, Siemens Healthcare Diagnostics, Marburg, Germany), PF1+2 (Enzygnost F 1+2 monoclonal, Siemens Healthcare Diagnostics), kallikrein (Plasma Kallikrein 1B Human SimpleStep ELISA kit, Abcam, Cambridge, UK) and FXIIa (Human Activated Coagulation Factor XII ELISA kit, Cryopep, Montpellier, France). FXIa was measured using a chromogenic assay (Biophen Factor XIa, Hyphen Biomed, Neuville-sur-Oise, France). All samples were measured in duplicate on stored plasma samples. Assays were performed according to manufacturer instructions.

Statistical Analysis Plan

Continuous variables are presented by median and interquartile range (25th–75th percentile), or range. The arithmetic mean of the 3 predialysis measurements (t0) was calculated as the baseline biological value for every individual dialysis patient. Categorical variables are described by absolute counts or proportions. The paired Wilcoxon signed-rank test, between the t240 and t5 values, was used to evaluate the evolution over time. Differences between membranes were evaluated by paired Wilcoxon signed-rank test comparing t240 biological results and delta values (t240–t5) between study sessions. Comparison between patients and healthy controls was performed using the Mann-Whitney U test. All statistical analyses were performed using STATA/IC 15.1 (StataCorp, College Station, TX).

Table 1. Baseline coagulation activation in chronic hemodialysis patients (n = 10) and healthy controls (n = 20)

Coagulation marker	Patients[a]	Healthy controls	z value	*P* value
TAT (mcg/l)	3.3 (2.9–4.2)	2.4 (2.3–2.5)	3.77	0.0002
PF1+2 (pmol/l)	647 (478–737)	138 (125–254)	4.31	<0.0005
FXIIa (pg/ml)	107 (90–287)	297 (143–1670)	−1.94	0.053
Kallikrein (mcg/ml)	157 (136–181)	174 (148–190)	−0.84	0.4
FXIa (mIU/ml)	0.57 (0.48–0.65)	0.76 (0.69–0.81)	−3.17	0.001

FXIa, activated factor XI; FXIIa, activated factor XII; PF1+2, prothrombin fragment 1+2; TAT, thrombin–antithrombin complex.

[a] Baseline values were calculated as the arithmetic mean of the 3 predialysis measurements for every hemodialysis patient. Predialysis values for all factors did not differ significantly among the 3 dialysis sessions with different membranes ($P > 0.05$ for all comparisons with Wilcoxon signed-rank test).

All results are presented as median (interquartile range), unless otherwise indicated.

RESULTS

Patient Population

Ten hemodialysis patients (3 women) completed the 3 study sessions between May and July 2017. Median age was 77 years (interquartile range, 72–78 years). Patients suffered from ischemic (n = 3), diabetic (n = 3), and tubulointerstitial nephropathy (n = 2); focal and segmental glomerulosclerosis (n = 1); and postrenal failure (n = 1). Median dialysis vintage was 5 years (interquartile range, 2.3–9.1 years; range, 1.1–12.6 years).

Baseline Coagulation Activation in Hemodialysis Patients

Hemodialysis patients showed significantly higher baseline thrombin generation markers compared to healthy controls (Table 1). Contact system markers FXIIa and kallikrein did not differ significantly between dialysis patients and healthy controls, whereas baseline FXIa levels were significantly lower in dialysis patients ($P = 0.001$; Table 1). There was no significant difference in the baseline levels of all the investigated coagulation factors among the 3 dialysis sessions using different membranes.

Coagulation Activation During Hemodialysis

A significant increase in TAT levels was noted for the 3 different hemodialysis membranes at t240 compared to t5 (Table 2; Figure 2; $z = -2.8$ with $P = 0.005$ for PP, $z = -2.2$ with $P = 0.03$ for PMMA, and $z = -2.7$ with $P = 0.008$ for AN69ST). Absolute TAT generation at the end of the dialysis sessions as well as TAT increase during dialysis were significantly lower during dialysis

Table 2. Coagulation activation during hemodialysis, including markers of contact system activation (n = 10)

Coagulation marker	Dialyzer membrane	t0	t5	t15	t30	t90	t240
TAT (mcg/l)	PP	3.3 (2.9–3.9)	3.2 (2.9–3.9)	2.9 (2.8–3.5)	3.4 (3.0–3.9)	6.3 (5.2–9.2)	9.0 (4.5–17.4)^{a,b}
	PMMA	4.3 (3.6–4.9)	3.4 (3.0–3.8)	3.5 (3.1–3.7)	3.1 (2.8–3.6)	4.2 (3.0–5.5)	5.5 (3.6–8.8)^{a,b}
	AN69-ST	4.3 (3.1–7.0)	3.3 (2.8–4.2)	3.2 (2.8–4.0)	3.7 (3.5–3.9)	5.3 (3.2–7.3)	7.2 (4.6–13.3)^{a,b}
PF1+2 (pmol/l)	PP	618 (531–685)	615 (490–669)	640 (536–709)	633 (478–691)	794 (531–853)	785 (511–1094)
	PMMA	729 (474–1044)	551 (453–852)	582 (475–772)	552 (472–736)	606 (451–751)	649 (435–780)
	AN69-ST	749 (445–780)	664 (491–761)	712 (431–801)	668 (462–791)	688 (406–899)	715 (627–1011)
FXIIa (pg/ml)	PP	113 (82–335)	118 (90–415)	112 (62–422)	125 (82–303)	117 (87–307)	113 (89–448)
	PMMA	123 (84–231)	109 (81–268)	112 (87–290)	112 (91–308)	112 (71–343)	116 (82–289)
	AN69-ST	109 (68–303)	118 (96–328)	112 (87–347)	120 (92–318)	120 (95–345)	119 (88–356)
Kallikrein (mcg/ml)	PP	185 (129–191)	162 (113–185)	158 (127–221)	178 (147–254)	178 (148–257)	163 (144–204)
	PMMA	141 (121–176)	162 (131–204)	152 (128–186)	147 (132–195)	163 (138–210)	171 (131–215)
	AN69-ST	171 (126–179)	180 (115–225)	171 (137–214)	160 (132–218)	174 (153–211)	167 (146–185)
FXIa (mIU/ml)	PP	0.55 (0.49–0.64)	0.57 (0.47–0.63)	0.51 (0.46–0.6)	0.54 (0.48–0.6)	0.51 (0.46–0.61)	0.54 (0.47–0.59)
	PMMA	0.60 (0.49–0.7)	0.56 (0.5–0.65)	0.51 (0.45–0.6)	0.57 (0.48–0.66)	0.54 (0.51–0.66)	0.57 (0.53–0.7)
	AN69-ST	0.55 (0.47–0.66)	0.53 (0.44–0.68)	0.53 (0.47–0.68)	0.53 (0.47–0.69)	0.55 (0.45–0.76)	0.55 (0.48–0.61)

AN69-ST, polyethylenimine-coated polyacrylonitrile dialyzer; FXIa, activated factor XI; FXIIa, activated factor XII; PF1+2, prothrombin fragment 1+2; PP, polyphenylene dialyzer; PMMA, polymethylmetacrylate dialyzer; TAT, thrombin–antithrombin complex.

[a] Testing of the null hypothesis as compared to t5 ($P = 0.005$ for PP, $P = 0.03$ for PMMA, and $P = 0.008$ for AN69ST with Wilcoxon signed-rank test).

[b] Between-dialyzer differences at t240 ($P = 0.04$ for PP vs. PMMA, $P = 0.8$ for PP vs. AN69ST, $P = 0.009$ for PMMA vs. AN69ST with Wilcoxon signed-rank test).

Results are presented as median (IQR). t followed by number indicates minutes after dialysis start.

using the PMMA dialyzer compared to PP and AN69ST membranes: z = −2.1 with $P = 0.04$ and z = −2.6 with $P = 0.009$ for TAT t240 values, and z = −2.1 with $P = 0.04$ and z = −2.4 with $P = 0.02$ for deltaTAT (t240–t5), respectively (Table 2). Post-dialysis thrombin generation markers TAT and PF1+2 correlated strongly for all membranes (Spearman rho = 0.93, 0.76, and 0.90 for PP, PMMA, and AN69ST dialyzer sessions, respectively).

Of interest, our data show no TAT increase at 30 minutes after dialysis start. The first increase of TAT is noted for the 90-minutes sample. All patients completed the scheduled 4-hour treatment time without macroscopic clotting of the extracorporeal circuit. Furthermore, all patients had adequate online dialysis adequacy monitoring (mean [interquartile range] online Kt/V 1.4 [1.2–1.7]) as an additional surrogate marker for efficient anticoagulation of the extracorporeal circuit.

Contact System Activation During Hemodialysis

Levels of FXIIa, kallikrein, and FXIa did not change during hemodialysis with any of the 3 dialyzer membranes (Table 2; Supplementary Figure S1). Kallikrein and FXIa levels were measured as surrogate outcome parameters of contact system activation, given that FXIIa activates FXI to FXIa and initiates the kallikrein–kinin system with cleavage of prekallikrein to kallikrein. A large inter-individual variability was noted for FXIIa, both in patients (range, 48–2717 pg/ml) and healthy controls (range, 97–2806 pg/ml). Patients with high levels of FXIIa had these during the 3 consecutive dialysis sessions (Supplementary Figure S1).

DISCUSSION

Patients included in the study, treated with maintenance hemodialysis using a well functioning arteriovenous fistula to access the dialysis circuit, present increased coagulation activation markers prior to the start of a hemodialysis session, in line with previous results regarding TAT[18] and PF1+2.[19] Higher baseline thrombin generation in patients treated with hemodialysis compared to peritoneal dialysis has been shown previously,[20] suggesting a role for the repetitive contact of blood with the extracorporeal circuit. Acknowledging the proinflammatory effects of thrombin, including endothelial inflammation and atherosclerosis,[21,22] these findings relate well with the known burden of inflammation and cardiovascular comorbidity in hemodialysis patients.[23]

During the studied dialysis treatments, an empirical anticoagulant regimen[24] was administered, establishing a clinically successful anticoagulant effect throughout the dialysis session, as shown by the absence of macroscopic clotting complications, and adequate online clearance results. The increase of TAT at 90 minutes after dialysis start in our study, irrespective of the dialyzer membrane used, suggests a late-onset threshold for thrombin generation, between 30 and 90 minutes after dialysis start, which is well before the treatment effect of the UFH is expected to have faded. Our results are in line with previous studies that have shown thrombin generation during hemodialysis, even if systemic anticoagulation was administered and sufficient for maintaining extracorporeal circuit patency.[3,19] These

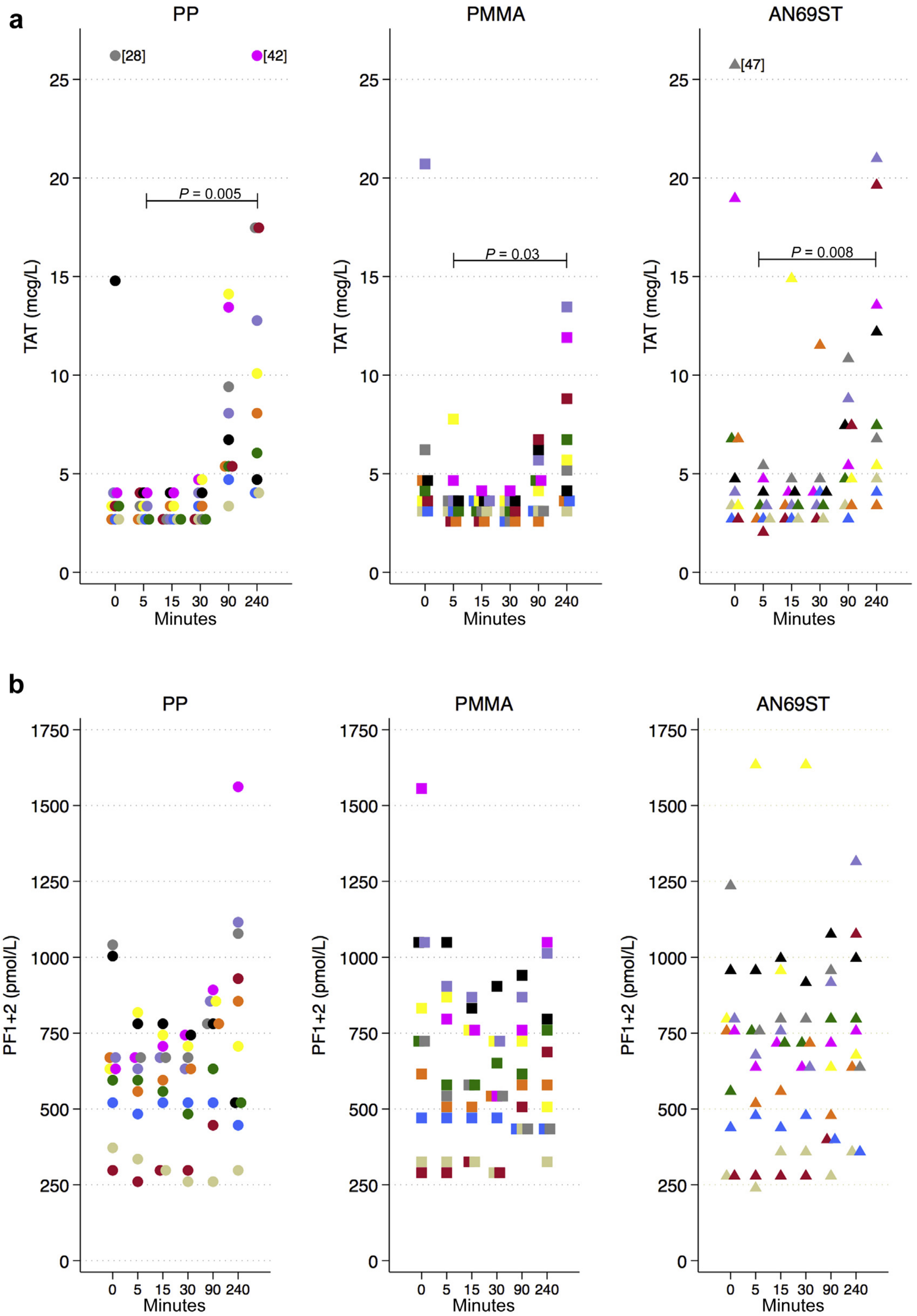

Figure 2. Thrombin generation during hemodialysis using different dialyzers. (a) Thrombin–antithrombin complex (TAT) generation and (b) prothrombin fragment 1+2 (PF1+2) generation during hemodialysis. Three outlier values with absolute values shown in brackets are not to scale. AN69-ST, polyethylenimine-coated polyacrylonitrile dialyzer; PMMA, polymethylmetacrylate dialyzer; PP, polyphenylene dialyzer.

previous studies either assessed coagulation-activation markers only up to 150 minutes after dialysis start[19] or lacked data on early coagulation-marker evolution.[3]

Despite the difference in thrombin generation markers between patients and controls, no difference in baseline values of the specific contact system markers FXIIa and kallikrein could be identified between the 2 groups, whereas FXIa was significantly lower in dialysis patients. UFH has a short half-life and no detectable activity shortly after the end of dialysis. Therefore, no antithrombin-mediated heparin-related effect is expected as the cause of low predialysis FXIa levels. Amplification of coagulation activation results, among other pathways, from thrombin-mediated FXI activation.[25] Ongoing thrombin generation, documented by increased baseline TAT and PF1+2 levels, will therefore cause an ongoing FXI activation, without affecting FXIIa and kallikrein generation. Although speculative, the ongoing FXI activation might lead to ongoing FXIa inactivation by known inhibitors of FXIa,[26] such as C1-inhibitor, alpha 2-antiplasmin, and alpha 1-antitrypsin, thereby lowering baseline FXIa levels.

The anticoagulant effect of UFH is established by potentiating the inhibitory actions of antithrombin on FXa and thrombin, and to a lesser extent on FXIa and FXIIa.[27] It seems unlikely that the heparin administration itself hampered FXIIa generation, and by extension, generation of FXIa and kallikrein. Absence of FXIIa increase has been observed during *in vitro* hemodialysis sessions using polysulphone membrane,[28] similar to our results. Moreover, this *in vitro* hemodialysis model showed thrombin generation despite using FXII-deficient blood.[28] However, no *in vivo* data are available to date on the kinetics of contact system markers during *in vivo* hemodialysis treatments. The absence of an increase in FXIIa, kallikrein, and FXIa during the hemodialysis sessions, and the delay in TAT increase, argue for a continuous activation of platelets[1] and leukocytes[6,7] being the main driving force for the generation of thrombin during hemodialysis, rather than a contact system–associated coagulation activation and amplification due to contact of blood with the extracorporeal circuit, which is established from dialysis start. Indeed, if it did occur, contact system–induced thrombin generation should be measurable within minutes. Stable TAT levels up to 30 minutes after dialysis start argue against effective coagulation activation induced by contact system activation during hemodialysis.

The differences between TAT and PF1+2 dynamics are in line with previously published results.[19] Dialysis treatments were standardized except for dialyzer membrane. Hence, the differences between membranes are most likely due to differences in physicochemical characteristics. Whether these differences are clinically meaningful needs further study.

Analysis costs and the exploratory set-up of the trial drove the small sample size and design of the study. A more comprehensive evaluation of the coagulation activation over a longer time period of hemodialysis treatment would be of interest. The most important limitation of our study is the impossibility of determining whether contact system activation is present but not measurable, or really absent. Our results cannot differentiate between true lack of activation and lack of increased expression, due to adsorption onto the dialyzer membrane, for example, or lack of test sensitivity. A recent study evaluating the use of a recombinant anti-FXII-antibody during extracorporeal membrane oxygenation therapy in rabbits showed efficient thromboprotection by the anti-FXII-antibody compared to heparin, despite the absence of detectable FXIIa in plasma of both treatment groups.[29] Similarly, the Ixodes Ricinus contact phase inhibitor (Ir-CPI), which inhibits both FXIIa and FXIa, was as efficient as UFH in preventing clot formation during cardiopulmonary bypass with cardiac surgery in sheep.[30] Although extracorporeal membrane oxygenation and cardiopulmonary bypass therapy differs significantly from dialysis, a study evaluating functional effects of a contact system inhibitor during *in vivo* hemodialysis would be of interest. Such a clinical trial, however, will be feasible only once these novel drugs become approved for human use.

CONCLUSION

Driven by the recent interest in the therapeutic options of specific contact system inhibitors, we aimed to evaluate contact system activation during *in vivo* hemodialysis. Chronic hemodialysis patients dialyzed through an arteriovenous dialysis access show coagulation activation during hemodialysis, marked by increased TAT and PF1+2 levels, despite using systemic anticoagulation to prevent macroscopic clotting of the extracorporeal circuit. The increase in thrombin generation markers was delayed until 90 minutes after hemodialysis start and was not associated with measurable contact system activation, assessed by FXIIa, kallikrein, and FXIa. Our results argue against effective contact system activation during hemodialysis and generate the hypothesis that novel specific contact system inhibitors alone might not suffice as anticoagulant treatment during hemodialysis.

DISCLOSURE

All the authors declared no competing interests.

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Our article is an original paper approved by all authors, who are affiliated with the Vrije Universiteit Brussel. The study protocol was registered at ClinicalTrials.gov, NCT 03090984. The results have not been published previously in whole or part, except in abstract form at the International Society of Nephrology World Congress of Nephrology 2019, Melbourne, April 12–15, 2019, at the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) meeting, 2019, Budapest, June 13–16, 2019, and at the International Society on Thrombosis and Haemostasis (ISTH) meeting, 2019, Melbourne, July 5–10, 2019. The manuscript is not under consideration for publication by another journal.

AUTHOR CONTRIBUTIONS

KF, CT, WC, and KMW designed the study. KF and VDM recruited patients, carried out the hemodialysis study treatments, and revised intellectual content. CO and KJ revised intellectual content and carried out the biological analyses. KF and KMW analyzed the data. KF, CT, and KMW drafted and revised the paper. All authors approved the final version of the manuscript and are accountable for the accuracy and integrity of the work.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

CONSORT Statement.

Figure S1.

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