Original Article

Coagulation, fibrinolysis and fibrinolysis inhibitors in haemodialysis patients: contribution of arteriovenous fistula

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Abstract

Background. End-stage renal disease (ESRD) patients, not uncommonly, might exhibit thrombotic complications, as well as they may present with a bleeding diathesis. Changes in vessel wall and/or blood flow in native arteriovenous fistula (AVF) might also augment these disarrangements, as vascular endothelium is predominantly involved in the regulation of haemostatic pathways.

Objective. This study was designed to evaluate the state of coagulation and fibrinolysis and the role of AVF on haemostatic defects, in ESRD patients on maintenance haemodialysis.

Methods. Plasma samples for prothrombin fragment 1+2, thrombin–antithrombin III complex, plasmin-α_2 antiplasmin complex, tissue type plasminogen activator antigen, urokinase type plasminogen activator antigen, u-PA activity, plasminogen activity, α_2-antiplasmin and α_2-macroglobulin assays were obtained from AVF and contralateral large veins of ESRD patients and from peripheral veins of the control group.

Results. Our results indicate a predominant thrombotic state as evidenced by activated coagulation markers and enhanced fibrinolysis in systemic circulation of ESRD patients. However the most novel finding is the probable contribution of AVF on haemostatic activation, as proven by the statistically different and positively correlated concentrations of both coagulation, fibrinolysis, and fibrinolysis inhibitors in AVF when compared to the levels in peripheral venous circulation.

Conclusion. In addition to systemic derangements of haemostasis in ESRD patients, AVF individually might have a substantial role in the modulation of coagulation and fibrinolytic cascade.

Key words: arteriovenous fistula; coagulation; fibrinolysis; fibrinolysis inhibitors; haemodialysis

Introduction

End-stage renal disease (ESRD) is assumed to possess a high risk for thrombotic complications such as

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ischaemic heart attacks, stroke, and thrombosis of arteriovenous fistula (AVF) in which this thrombotic state is a predominant cause of mortality in the vast majority of patients on maintenance haemodialysis programmes [1,2]. On the other hand, ESRD patients may rather present with a contrasting clinical picture of a bleeding diathesis which is mainly caused by functional platelet abnormality and defective platelet adhesion to vessel walls [3–5]. Although severe bleeding complications such as cerebral haemorrhages and haemopericardium are rare, excessive bleeding following a trauma and eventual blood loss during surgery poses a clinical problem [6]. These peculiar haemostatic defect(s) are associated with a high morbidity in such a way that thrombotic complications related to AVF still account for nearly 30% of all hospital admissions of haemodialysis patients [7,8]. An additional consideration, however, is the changes in morphology of vessel wall and blood flow in the created native AVF that might contribute to haemostatic disarrangement observed in uraemic patients, since vascular endothelium is actively involved in haemostasis [9,10].

The alteration of functional and morphological state in AVF may play a putative role in the abnormality of haemostasis in uraemic patients. We studied haemostatic and fibrinolytic parameters in venous plasma samples of ESRD patients and compared to that of healthy controls to assess the haemostatic defects in uraemia. Furthermore, plasma samples obtained from contralateral veins of patients and from venous return of AVF were measured to determine whether haemostasis and fibrinolysis are locally activated in AVF. The aim of this study is therefore to assess the molecular markers leading to activation and/or inhibition of coagulation and fibrinolysis in ESRD patients and to evaluate the possible contribution of AVF on these haemostatic parameters.

Subjects and methods

Patients

Patients with a history of thrombosis (including thrombosis of fistula, myocardial infarction or deep venous thrombosis)

or a haemorrhagic event within last 6 months, and those with a history of malignancy, amyloidosis, diabetes mellitus or a documented infection were not included in the study. Twenty-six ESRD patients (18 male, 8 female, mean age $\pm$ SD: 39.3 ± 11.4, range: 21–69) were eligible after initial evaluation. The causes of ESRD in the study group were chronic glomerulonephritis in 12 patients, chronic pyelonephritis in eight, polycystic kidney disease in two, and of unknown origin in four. They have been maintained on chronic haemodialysis programmes for an average of 71.7 ± 22.4 months (range 28–106). Patients have been dialysed for 4–5 h each day, 3 days a week using hollow-fibre dialysers made of cuprophane. Bicarbonate-based dialysate was used in 14 patients while acetate-buffered dialysate was used in the remaining 12. In all patients haemodialysis procedure was performed by means of an AVF created in one of the upper extremities, with a blood flow maintained at least 200 ml/min and without an anatomical lesion (confirmed by Doppler ultrasonography and fistulography). Mean duration of AVFs of patients was 27.1 ± 11.2 months. None of the patients was HBsAg positive. Although 11 were seropositive for hepatitis C (HCV), their serial ALT measurements had been within normal limits for the last 6 months. Patients were administered calcium carbonate as phosphate binders, and iron and multivitamin supplementation, essential amino acids, and antihypertensive medication when indicated. Sodium, potassium, phosphorus and fluid restrictions were recommended if needed. Fourteen patients were receiving recombinant human erythropoietin (rHuEpo) treatment 50–100 U/kg per week. Patients receiving medications known to interfere with haemostasis (i.e. oral contraceptives, antiaggregants), except for heparin administered during haemodialysis session and rHuEpo were not enrolled to the study.

Control group

The control group consisted of 22 healthy normal volunteers, mainly hospital staff (12 male, 10 female, mean age 37.1 ± 9.2, range 20–58). They had normal renal function, had no evidence of systemic disease, including infection, and had not received any kind of medication.

Assays

The study was a cross-sectional determination of prothrombin fragment 1+2 (PF 1.2), thrombin-antithrombin III complex (TAT), plasmin-α_2 antiplasmin complex (PAP), tissue type plasminogen activator antigen (tPA Ag), urokinase type plasminogen activator antigen (uPA Ag), u-PA activity (uPA Act), plasminogen activity (PLG act), α_2-antiplasmin (α_2-AP), and α_2-macroglobulin (α_2-M) concentrations in plasma samples taken simultaneously from venous return of AV fistulae, large veins of contralateral upper extremity of haemodialysis patients, and from large antecubital veins of healthy volunteers. Blood specimens were obtained from patients just before a haemodialysis session. Each test procedure started between 8:00 and 8:30 a.m., in order to avoid the effects of diurnal variation of the haemostatic system. Blood samples were drawn after a 30-min period of rest in the sitting position by 19-G butterfly needle connected with a plastic syringe without interruption of venous flow. Twelve millilitres of blood were drawn at each sampling time with the first few millilitres discarded. Nine millilitres of each sample were put into polypropylene tubes containing 1 ml 0.109 M trisodium citrate and centrifuged at

Table 1. Assays used for the quantitative measurement of the parameters

Prothrombin fragment 1+2	Enzygnost® F 1+2 micro enzyme immunoassay, Behringwerke AG, Germany
Thrombin–antithrombin III complex	Enzygnost® TAT micro enzyme immunoassay, Behringwerke AG, Germany
Plasmin-α_2 antiplasmin complex	EIA APP micro enzyme immunoassay, Behringwerke AG, Germany
t-PA antigen	ELISA, Tintelize® t-PA, Biopool, Sweden
u-PA antigen	ELISA, Tintelize® u-PA, Biopool, Sweden
u-PA activity	Chromogenic Assay, Chromolyse™ uPA, Biopool, Sweden
Plasminogen activity	Chromogenic Assay, Spectrolyse® Plasminogen SK, Biopool, Sweden
α_2-Antiplasmin	Stachrom® Antiplasmin, Colorimetric Assay of Antiplasmin, Diagnostica Stago, France
α_2-Macroglobulin	NOR-Partigen®, Immunodiffusion plates for quantitative protein determinations of α_2-macroglobulin, Behring, Germany

3000 r.p.m. for 15 min at $+10$ to $+18°C$, the supernatant plasma samples obtained were transferred into polypropylene tubes and stored at $-30°C$ until assayed.

PF 1.2, TAT, PAP, tPA Ag, uPA Ag, concentrations in plasma samples were measured by the solid phase 'sandwich' enzyme-linked immunosorbent assay (ELISA) method. Quantitative uPA act, and PLG act levels in plasma samples were determined by chromogenic assays. α_2-AP concentrations of the same samples were determined by synthetic chromogenic substrate method and α_2-M levels were measured by radioimmunodiffusion method (Table 1).

All assay procedures were performed according to the manufacturers' recommendations in a single session in order to avoid interassay variations. Assays were performed in duplicate and the average of two measurements was used for statistical analysis. Intra-assay coefficients of variation for various assays performed in our laboratory were less than 8.8%. Calculations were done with a computer-based curve-fitting statistical software package.

Statistical analysis

To avoid a covariance effect, if any, we performed multivariate analysis of the studied haemostatic parameters taking each preassay characteristics (age, sex, type of dialysate used, duration of patent AVF, HCV positivity, or erythropoietin treatment) as a covariate in the model. The differences of haemostatic parameters between arteriovenous fistula and peripheral vein of haemodialysis patients were calculated by paired-sample t test, and independent samples t test was utilized for comparisons of venous samples between patient and control group. Correlations of haemostatic parameters amongst arteriovenous fistula

and peripheral vein in haemodialysis patients were measured by Pearson's correlation test. Positive results obtained from correlation analysis were tested to fit in a linear model by regression analysis. Results were expressed as mean±SEM and P values lower than 0.05 were reckoned to be significant. SPSS (Statistical Package for Social Sciences) v 5.01 for Windows were utilized to analyse the data.

Results

According to the results of multivariate analysis of preassay characteristics there were no difference in studied haemostatic parameters by means of age, sex, type of dialysate used (acetate vs bicarbonate), duration of patent AVF, HCV positivity, or erythropoietin treatment ($P > 0.05$). Prothrombin time, activated PTT, thrombin time, and platelet count were within normal limits before study and showed no statistically significant difference between patient and control groups ($P > 0.05$). Prior to the study, mean±SD haemoglobin concentration was found to be 9.1 ± 1.3 g/dl in the patient group.

Mean±SEM plasma concentrations and the results of the statistical comparisons of studied parameters in AVF and peripheral veins of uraemic patients on maintenance haemodialysis and that of healthy subjects are given in Table 2.

Coagulation markers

PF 1.2 and TAT, *in vivo* markers of coagulation, were found to be elevated in venous samples of patients comparing to control group. Besides *in vivo* coagulation was shown to be more pronounced in AVF of uraemic group as PF 1.2 and TAT were higher in AVF compared to samples of opposite vein.

Fibrinolytic parameters

The mean venous concentrations of uPA Ag and tPA Ag were similar between patient and control group,

while mean levels of uPA act were higher in ESRD patients. However, uPA Ag, uPA act, and tPA Ag were found to be increased in AVF compared to the levels of peripheral vein of the patient group similar to the results observed in coagulation markers. Moreover, haemodialysis patients revealed significantly elevated venous PAP and PLG act concentrations above those of the control group, and these parameters were also higher in AVF when compared to the mean levels of contralateral veins in the patient group.

Fibrinolysis inhibitors

Mean α_2-AP and α_2-M concentrations were comparable between study and control groups, but α_2-AP was found to be statistically low where mean α_2-M levels were significantly higher in AVF when compared to the levels of peripheral veins in uraemic patients.

Correlation between AVF and contralateral vein

All studied haemostatic parameters showed a significant correlation between AVF and contralateral peripheral vein, and furthermore both AVF and venous levels of each parameter exhibited a pattern of positive linear regression ($P < 0.05$) with regression lines having changing intercepts and slopes (Figure 1 A–D).

Discussion

Major determinants of the haemostatic systems consists of vascular endothelium, platelets, and proteins of coagulation and fibrinolytic system. The pathological and physiological activation of the haemostatic process could occur via the generation of several molecular markers of haemostasis before any clinically evident thrombotic event [11,12]. Coagulation and fibrinolytic markers have been studied previously in ESRD patients in connection with the effect of haemodialysis procedure and type of dialyser used [13–15]. However, the paucity of the literature makes it difficult to draw conclusions concerning the effect(s) of AVF
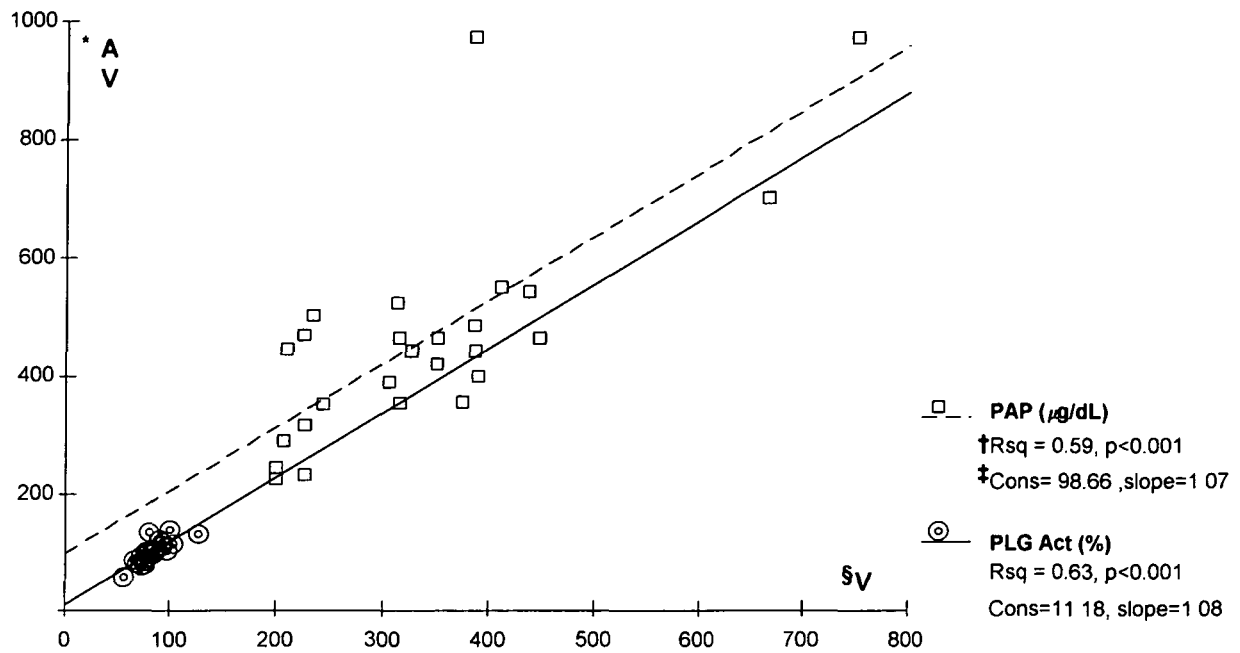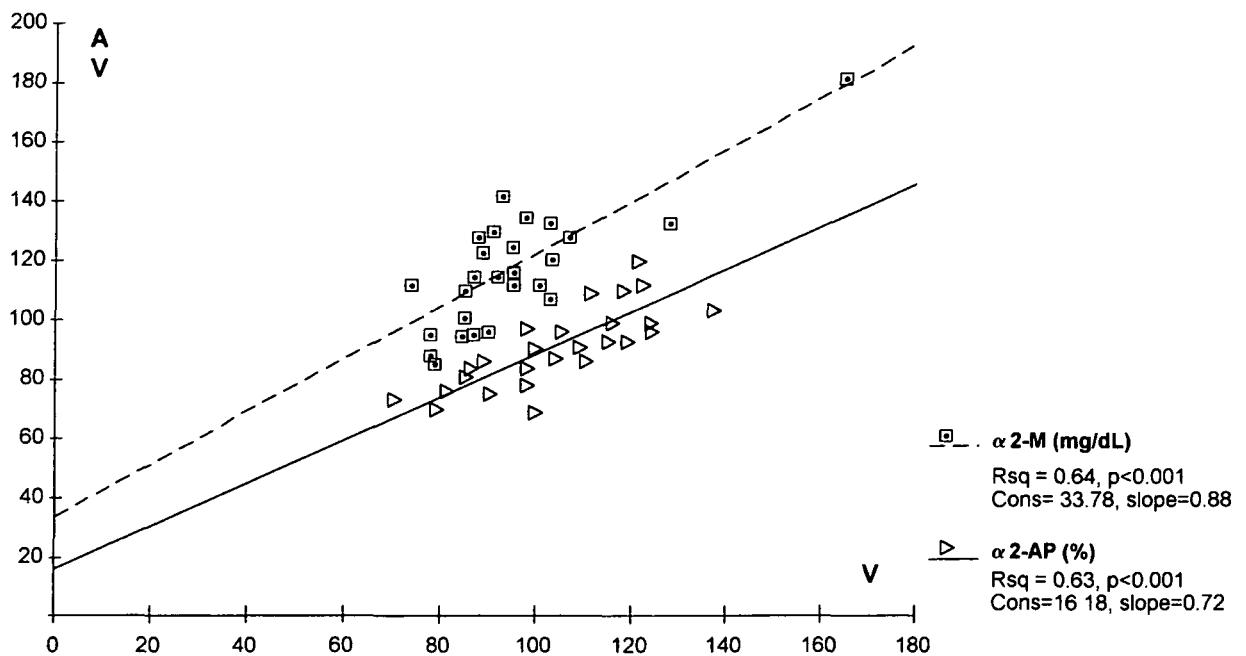
Table 2. Levels of haemostatic parameters in patient and control groups (Results in mean±SEM)

	Patient group				Controls
	AVF	P^*	Peripheral vein	$P\dagger$	
Prothrombin fragment 1+2 (nmol/l)	5.5±0.5	<0.001	3.3±0.2	<0.001	1.6±0 0.0
Thrombin–antithrombin III complex (µg/dl)	11.9±1.4	<0.001	4.5±0.6	<0.001	1.8±0 0.1
Plasmin–α_2 antiplasmin complex (µg/dl)	453.7±44.0	<0.001	329.7±31.2	0.017	247.4±7.2
t-PA antigen (ng/ml)	4.9±0.4	<0.001	2.6±0.4	NS ‡	2.2±0.1
u-PA antigen (ng/ml)	2.8±0.3	<0.001	1.3±0.1	NS	1.2±0.0
u-PA activity (ng/ml)	0.27±0.0	<0.001	0.18±0.0	<0.01	0.15±0.0
Plasminogen activity (%)	101.9±4.3	<0.001	83.4±3.2	<0.001	60.8±1.1
α_2-Antiplasmin (%)	91.2±2.7	<0.001	103.6± 2.9	NS	97.1±1.3
α_2-Macroglobulin (mg/dl)	117.6±4.6	<0.001	94.5±4.2	NS	90.4±1.4

*AVF vs peripheral vein in patient group (paired samples t test).
†Peripheral vein of patients vs controls (independent samples t test).
‡Not significant ($P > 0.05$).

A

PAP (µg/dL)
†Rsq = 0.59, p<0.001
‡Cons= 98.66 ,slope=1 07

PLG Act (%)
Rsq = 0.63, p<0.001
Cons=11 18, slope=1 08

B

α 2-M (mg/dL)
Rsq = 0.64, p<0.001
Cons= 33.78, slope=0.88

α 2-AP (%)
Rsq = 0.63, p<0.001
Cons=16 18, slope=0.72

on haemostasis. This possible effect deserves attention since changes in morphology of vascular endothelium and unusual increments in luminal blood flow may contribute in local activation of both coagulation and fibrinolysis.

PF 1.2 is a good indicator of thrombin, and once thrombin is formed it makes complexes with endogenous serine proteases such as antithrombin III [16]. The TAT complex, like PF 1.2, could be measured in blood during slight clotting activation [17]. These two markers of coagulation circulate in the blood of patients who suffer from any kind of thrombotic disorders [3]. *In vivo* activation of coagulation system in chronic renal failure is a well-known clinical entity; however, the exact mechanisms by which the thrombotic state develops in renal failure is not clear. In our study, PF 1.2 and TAT levels were found to be elevated in ESRD patients, consistent with previous reports [14,17]. Interestingly, enhanced thrombin generation documented by the increments of PF 1.2 and TAT
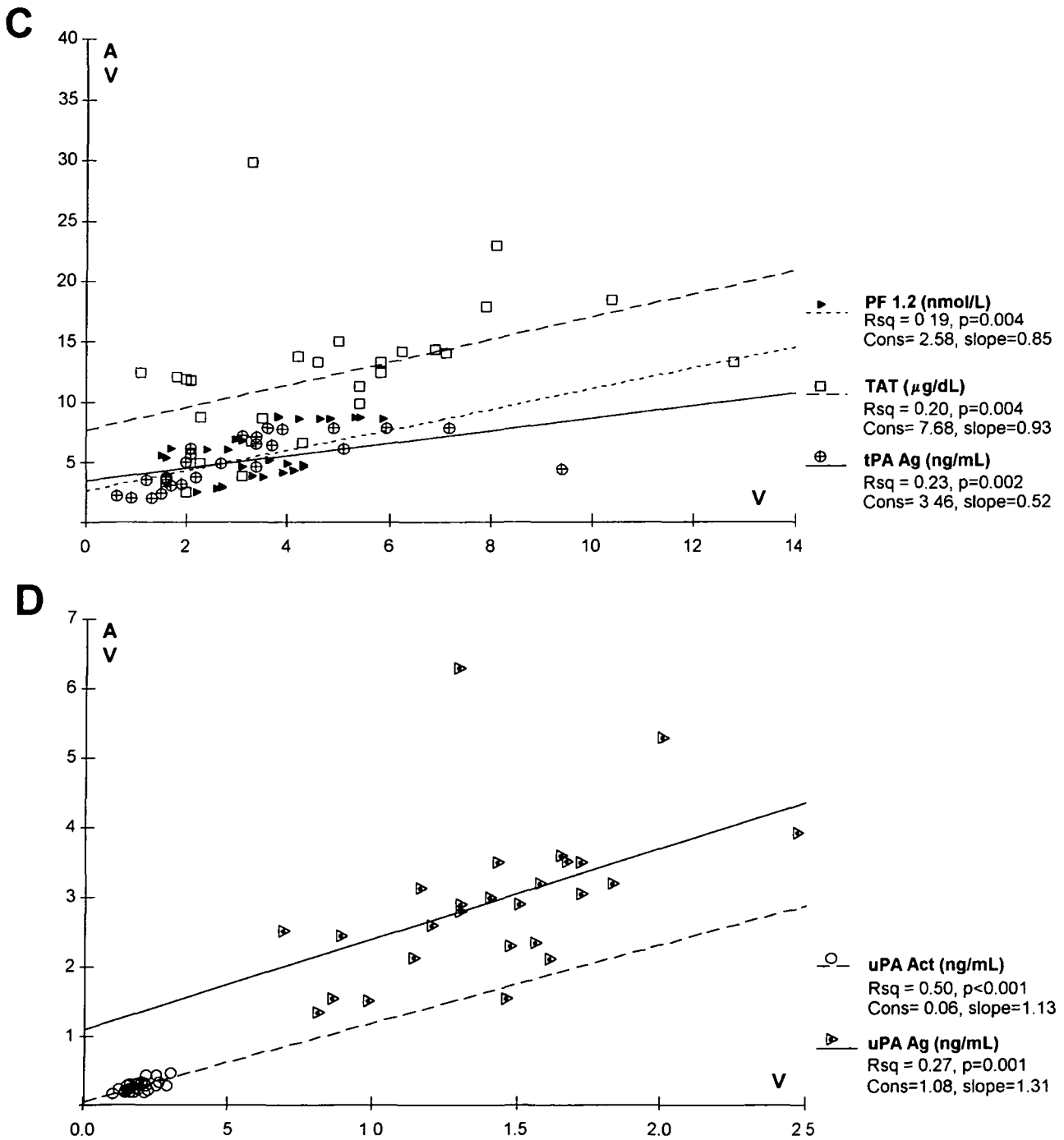
C

Plot with y-axis A/V from 0 to 40 and x-axis V from 0 to 14.

PF 1.2 (nmol/L)
Rsq = 0 19, p=0.004
Cons= 2.58, slope=0.85

TAT (μg/dL)
Rsq = 0.20, p=0.004
Cons= 7.68, slope=0.93

tPA Ag (ng/mL)
Rsq = 0.23, p=0.002
Cons= 3 46, slope=0.52

D

Plot with y-axis A/V from 0 to 7 and x-axis V from 0.0 to 2 5.

uPA Act (ng/mL)
Rsq = 0.50, p<0.001
Cons= 0.06, slope=1.13

uPA Ag (ng/mL)
Rsq = 0.27, p=0.001
Cons=1.08, slope=1.31

Fig. 1. Regression lines of haemostatic parameters between AVF* and contralateral vein[§] in haemodialsis patients (†R-square value, ‡intercept). A PAP (plasmin-α_2 antiplasmin complex) PLG act (plasminogen activity) B α_2-M (α_2-macroglobulin) α_2-AP (α_2-antiplasmin) C PF 1.2 (Prothrombin fragment 1+2) TAT (thrombin-antithrombin III complex) tPA Ag (tissue type plasminogen activator antigen) D uPA Act (u-PA activity) uPA Ag (urokinase type plasminogen activator antigen).

levels in AVF compared to that of contralateral veins may contribute significantly to the thrombotic state in ESRD patients. Keeping the fact of positive correlation of coagulation markers between AVF and contralateral peripheral vein in mind, it is noteworthy that AVF seems to play a crucial role in the pathogenesis of the thrombotic state in uraemia. To date, no such study

concerning the effect of AVF on coagulation activation has been reported.

There are two major types of plasminogen activators in circulating blood: tPA and uPA. Both reveal relatively weak activity in circulation, but are converted to more active forms when fibrin is formed. tPA, the main physiological activator of blood fibrinolysis, is

released from the blood vessels, facilitating the lysis of on-site fibrin clot where impairment of release results in thrombotic complications [18]. Likewise, uPA is secreted into the circulation from vascular endothelial cells and possesses a similar role in fibrinolysis [19]. As plasmin is generated, it is effectively inhibited by α_2-AP forming PAP complex, which is a another marker of activity status of the fibrinolytic system, and increments in concentrations reflect plasmin formation [20]. Fibrinolytic activity is found to be greatly enhanced in AVF of our patient group, since PAP, tPA Ag, uPA Ag, uPA act, and PLG act concentrations were significantly higher than the contralateral veins' measurements, and correlated positively. PAP, uPA act and as well as plasminogen activity were higher in the patient group compared to healthy controls, while tPA Ag and uPA Ag showed no significant difference. This observation is in keeping with a slightly increased fibrinolytic activity in ESRD patients. There have been conflicting data arguing no change [21], decrement [22], or increment [15] of fibrinolytic activity in uraemia. This controversy might be mainly due to variability in study design or methodology and different group of patients (i.e. age, underlying disease, or causes of ESRD). It might be hypothesized that as with increased thrombin generation in AVF, fibrinolysis is activated in the fistula and increased coagulation along with fibrinolysis in the AVF builds a dynamic balance that maintains the patency of the fistula. More activation of coagulative pathway and/or depression of fibrinolytic activity might lead to thrombosis of the fistula; however, at what point this critical equilibrium is broken has still to be elucidated.

Thrombi formed *in vivo* are subject to endogenous fibrinolysis and this process is hampered by the presence of α_2-AP, a primary inhibitor of plasmin activity, also hindering the absorption of plasminogen to fibrin and thereby retarding the initiation of the fibrinolytic process in which deficiency of α_2-AP leads a severe haemorrhagic tendency [23]. While α_2-M plays a secondary role in prevention of systemic fibrinolysis, it has a naturally occurring anticoagulant activity by inhibiting thrombin [24,25]. We did not observe any significant difference in peripheral venous α_2-AP and α_2-M concentrations between patient and control group. In spite of this observation, α_2-AP was significantly low and α_2-M was high in AVF, consistently with other studied parameters, as they revealed the same pattern of positive correlation between AVF and peripheral vein. Decreased levels of α_2-AP in haemodialysis patients obtained here have also been noted previously in particular reports, however with insufficient data concerning the source of sampling (artery or vein) in these studies [15,26]. Locally depression of α_2-AP levels in AVF compared to peripheral vein, along with enhanced fibrinolysis in our study, is a new observation that these findings might be used as a factor to prevent the thrombosis of a fistula. Nevertheless, it is certain that follow-up of patients for longer periods is necessary to resolve the conflict concerning the clinical implications of these *in vitro* haemostatic markers.

In conclusion both coagulation and fibrinolysis seem to be activated in ESRD patients, and additionally AVF might be an independent factor to interfere with and/or induce the haemostatic cascade activation, which warrant further studies to expand the knowledge related to abnormalities of haemostasis in haemodialysis patients.

References

1. Lindner A, Charra B, Sherrard DJ, Scribner BH. Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; 290: 697–702
2. Ansari A, Kaupke CJ, Vaziri ND, Miller R, Barbari A. Cardiac pathology in patients with end-stage renal disease maintained on hemodialysis. *Int J Artif Organs* 1993; 16: 31–36
3. Rabelink TJ, Zwaginga JJ, Koomans HA, Sixma JJ. Thrombosis and hemostasis in renal disease. *Kidney Int* 1994; 46: 287–296
4. Castillo R, Lozano T, Escolar G, Revert L, Lopez J, Ordinas A. Defective platelet adhesion on vessel subendothelium in uremic patients. *Blood* 1986; 68: 337–342
5. Escolar G, Cases E, Bastida M *et al.* Uremic platelets have a functional defect affecting the interaction of von Willebrand factor with glycoprotein IIb-IIIa. *Blood* 1990; 76: 1336–1340
6. Remuzzi G. Bleeding in renal failure. *Lancet* 1988; 1: 1205–1208
7. Chazan JA, London MR, Pono LM. The impact of diagnosis-related groups on the cost of hospitalization for end-stage renal disease patients at Rhode Island Hospital from 1987 to 1990. *Am J Kidney Dis* 1992; 6: 523–525
8. Chazan JA, London MR, Pono LM. Long-term survival of vascular accesses in a large chronic hemodialysis population. *Nephron* 1995; 69: 228–233
9. Remuzzi G, Cavenaghi A, Mecca G, Donati M, DeGaetano G. Prostacyclin-like activity and bleeding in renal failure. *Lancet* 1977; 2: 1195–1197
10. Remuzzi G, Perico N, Zoja C, Corna D, Macconi D, Vigano D. Role of endothelium derived nitric oxide in the bleeding tendency of uremia. *J Clin Invest* 1990; 86: 1768–1771
11. Fareed J, Walenga JM, Bick RL *et al.* Low molecular weight markers of hemostatic defects: impact of automation on the quantitation of hemostatic disorders. *Semin Thromb Hemost* 1983; 9: 354–378
12. Fareed J, Bick RL, Hoppensteadt DA, Bermes EW. Molecular markers of hemostatic activation: applications in the diagnosis of thrombosis and vascular and thrombotic disorders. *Clin Appl Thromb Hemost* 1995; 1: 87–102
13. Sultan Y, London GM, Goldfarb B, Toulon P, Marchais SJ. Activation of platelets, coagulation and fibrinolysis in patients on long-term hemodialysis: influence of cuprophan and polacrylonitrile membranes. *Nephrol Dial Transplant* 1990; 5: 362–368
14. Sagripanti A, Cupisti A, Baicchi U, Ferdeghini M, Morelli E, Barsotti G. Plasma parameters of the prothrombotic state in chronic uremia. *Nephron* 1991; 63: 273–278
15. Nakamura Y, Chida Y, Tomura S. Enhanced coagulation-fibrinolysis in patients on regular hemodialysis treatment. *Nephron* 1991; 58: 201–204
16. Hursting MJ, Stead AG, Crout FV, Horvath BZ, Moore BM. Effects of age, race, sex, and smoking on prothrombin fragment 1. 2 in a healthy population. *Clin Chem* 1993; 39: 683–686
17. Deguchi K, Noguchi M, Yuwasaki E *et al.* Dynamic fluctuations in blood of thrombin/antithrombin III complex (TAT). *Am J Hematol* 1991; 38: 86–89
18. Aoki N. Hemostasis associated with abnormalities of fibrinolysis. *Blood Rev* 1989; 3: 11–17
19. Wijngaards G, Kluft C, Groeneveld E. Demonstration of urokinase-related fibrinolytic activity in human plasma. *Br J Haematol* 1982; 51: 165–169
20. Moroi M, Akoi N. Isolation and characterization of alpha-2-plasmin inhibitor from human plasma. *J Biol Chem* 1976; 251: 5956–5965
21. Brommer EJP, Schicht I, Wijngaards G, Verheijen JH, Rijken

DC. Fibrinolytic activators and inhibitors in terminal renal insufficiency and in anephric patients. *Thromb Haemost* 1984; 52: 311–314

22. Taylor JE, Belch JJF, McLaren M, Henderson IS, Stewart WK. Effect of erythropoietin therapy and withdrawal on blood coagulation and fibrinolysis in hemodialysis patients. *Kidney Int* 1993; 44: 182–190

23. Aoki N, Sakata Y, Matsuda M, Tateno K. Fibrinolytic states in a patient with congenital deficiency of alpha-1-plasmin inhibitor. *Blood* 1980; 55: 483–488

24. Harpel PC, Mosesson MW. Degradation of human fibrinogen by plasma α-2 macroglobulin-enzyme complexes. *J Clin Invest* 1973; 52: 2175–2179

25. Fischer AM, Tapon-Bretaudiere J, Bros A, Josso F. Respective roles of antithrombin III and alpha 2 macroglobulin in thrombin inactivation. *Thromb Haemost* 1981: 45: 51–56

26. Vaziri ND, Gonzales EC, Wang J, Said S. Blood coagulation, fibrinolytic and inhibitory proteins in end-stage renal disease: effects of hemodialysis. *Am J Kidney Dis* 1994; 23: 828–835