

Fibrinolytic Potential and Antiphospholipid Antibodies in Systemic Lupus Erythematosus and Other Connective Tissue Disorders

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Summary

We studied the fibrinolytic response before and after venous occlusion (VO) in 30 patients with systemic lupus erythematosus (SLE), 25 with rheumatoid arthritis (RA) and 25 with different connective tissue disorders. Results were compared in patients with and without antiphospholipid antibodies (APA) and a history of either thrombosis or abortions. Before occlusion plasma levels of tissue-type plasminogen activator (t-PA) antigen and its inhibitor (PAI-1) were significantly higher in the patient group ($p < 0.001$). After occlusion, a low fibrinolytic activity on fibrin plates ($p < 0.005$) was observed in the same group. t-PA capacity and t-PA release were similar in relation to controls. The plasma PAI-1 activity was significantly elevated in each group of patients ($p < 0.005$) as compared to the control group. No significant differences with respect to t-PA and PAI-1 were observed in patients as to the presence or absence of thrombosis. There was also no correlation between the fibrinolytic changes and the presence of APA. It is concluded that an impairment of the fibrinolytic system, mainly related to increased PAI-1 levels, is present in most patients with connective tissue disorders, although these changes did not correlate with the presence of APA or the incidence of thrombosis.

Introduction

Lupus anticoagulant (LA) and anticardiolipin antibodies (ACA) are closely related antiphospholipid antibodies (APA) which are associated with a range of clinical manifestations, including recurrent thromboembolism, recurrent fetal loss and immune thrombocytopenia (1).

These antibodies have been frequently associated with systemic lupus erythematosus (SLE), but they may be found in association with other autoimmune disorders as well as in patients with no detectable underlying disease, what is called primary antiphospholipid syndrome (2).

The mechanisms of thrombosis in patients with APA remain unclear. Whether APA represent an epiphenomenon or are the cause of thromboembolic complications is still unknown. Several reports have focused on decreased levels of prostacyclin, acquired coagulation antithrombin III, protein C and protein S deficiencies and decreased expression of thrombomodulin (3–6).

Alternatively abnormal fibrinolysis caused by reduced release of tissue plasminogen activator (t-PA) or increased plasminogen activator inhibitor (PAI-1) levels have been demonstrated in patients with SLE (7, 8). However, no clear relationship between these findings and the presence or absence of thrombosis or APA has been clearly established. On the other hand, data on

fibrinolysis parameters in patients with antiphospholipid antibodies have given contradictory results (9, 10).

Since impaired fibrinolysis is a contributing factor for the development of thrombosis (11, 12), we have investigated the fibrinolytic potential, as assessed by the response to a venous occlusion test using highly sensitive assays for activators and inhibitors of fibrinolysis, in a large series of patients with connective tissue diseases. Results were correlated with the presence of thrombotic episodes, recurrent abortions and antiphospholipid antibodies.

Patients and Methods

Patients

We studied 80 patients (mean age 49 ± 18 years) with connective tissue diseases (each of whom fulfilled the American Rheumatism Association criteria) diagnosed as SLE ($n = 30$), rheumatoid arthritis ($n = 25$) and a miscellaneous group of 25 patients (Behçet's syndrome = 5, dermatomyositis = 4, CREST syndrome = 5, Sjögren's syndrome = 3, systemic sclerosis = 2 and overlap syndrome = 6). The clinical characteristics as well as the history of thrombosis and abortion and the incidence of APA are shown in Table 1. Nineteen patients were considered to have clinical activity at the time of inclusion.

A control group consisted of 30 age-matched healthy subjects.

Blood Samples

Blood was collected in all patients after a 20 min period of rest between 9 a. m. and 11 a. m. Samples were taken before and 10 min after venous occlusion and collected into 0.1 vol trisodium citrate 0.11 M. After centrifugation for 15 min at $2,000 \times g$ and 4°C aliquots were stored at -70°C until used. An aliquot of plasma was spun for a further 15 min centrifugation for the lupus anticoagulant tests. A serum sample was taken for the measurement of ACA.

For the t-PA activity assay 4.5 ml samples were collected on Biopool Stabilite tubes (Biopool, Sweden) for acidification purposes. They were immediately centrifuged at $3,000 \times g$ for 20 min at 4°C and frozen at -70°C .

Methods

Antiphospholipid antibodies were determined by two methods:

- Specific assays for lupus anticoagulant included: kaolin clotting time (13), dilute Russell's viper venom time (14) and dilute thromboplastin time (15). A positive result was always confirmed by mixing experiments with normal plasma.
- Anticardiolipin antibodies were determined by an ELISA assay according to Loizou et al. (13) using the QACA ELISA kit (Cheshire Diagnostics Limited, Chester, UK). A positive ACA was considered to be IgG > 15 GPL or IgM > 12 MPL.

Before venous occlusion the following fibrinolysis parameters were determined:

- Euglobulin fibrinolytic activity (EFA) on fibrin plates (17).
- t-PA activity and PAI-1 activity were measured by amidolytic assays (Coaset t-PA and Coaset PAI respectively, KabiVitrum, Stockholm, Sweden).

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Table 1 Baseline characteristics of patients

	SLE (n = 30)	RA (n = 25)	Others (n = 25)
Male/female	2/28	7/18	7/18
Positive APA	12	17	9
Positive LA	10	14	5
Positive ACA	10	4	4
Abortion	10* (8)	3 (1)	1 (0)
Thrombosis	6 (5)	3 (3)	3 (1)
Active disease	6 (5)	11* (8)	2 (1)

* $p < 0.02$; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis. The number of patients with thrombosis, abortions or active disease and positive APA is shown between brackets.

Table 2 Fibrinolysis parameters in patients and controls. Results obtained before and after venous occlusion (VO) are included. Data are reported as mean \pm SD

	Patients	Controls	<i>p</i>
EFA (U/ml)			
- pre-VO	1.24 \pm 1.60	1.28 \pm 1.22	ns
- post-VO	15.97 \pm 21.10	35.39 \pm 27.89	0.003
Fibrinolytic response	14.44 \pm 20.33	34.10 \pm 27.74	0.002
t-PA activity (U/ml)			
- pre-VO	0.97 \pm 0.42	0.75 \pm 0.28	ns
- post-VO	11.95 \pm 11.95	10.28 \pm 5.05	ns
t-PA capacity (U/ml)	10.98 \pm 11.03	9.53 \pm 5.18	ns
t-PA Ag (ng/ml)			
- pre-VO	11.50 \pm 6.24	4.86 \pm 26.30	<0.0001
- post-VO	26.97 \pm 15.33	19.56 \pm 13.51	0.03
t-PA release (ng/ml)	15.31 \pm 13.01	14.70 \pm 12.49	ns
PAI-1 activity (U/ml)			
- pre-VO	18.17 \pm 10.35	6.56 \pm 4.89	<0.001
- post-VO	8.94 \pm 10.50	1.35 \pm 1.83	0.001
PAI-1 Ag (ng/ml)	29.83 \pm 22.40	12.99 \pm 9.68	<0.001
Fibrinogen (mg/dl)	420.14 \pm 111.34	323.64 \pm 67.14	0.002
Plasminogen (%)	96.72 \pm 28.70	90.72 \pm 14.86	ns
α_2 -AP (%)	106.58 \pm 8.64	99.72 \pm 8.94	ns

- t-PA antigen (t-PA Ag) and PAI-1 antigen (PAI-1 Ag) were measured by ELISA assays using commercially available kits (TintElize t-PA and TintElize PAI-1 from Biopool, Sweden).
- Plasminogen and alpha-2-antiplasmin (α_2 -AP) were measured by amidolytic assays (Coatest Plasminogen and Coatest Antiplasmin, KabiVitrum, Stockholm, Sweden).
- Fibrinogen was determined by a standard clotting assay.

After occlusion EFA, t-PA activity and antigen and PAI-1 activity were determined in all samples.

The fibrinolytic response was defined as the difference between EFA after and before venous occlusion. t-PA capacity was defined as the difference between t-PA activity before and after occlusion. t-PA release was calculated as the difference between postocclusion and preocclusion values for t-PA Ag as described by Hamsten et al. (18).

Statistics

The non-parametric Mann-Whitney U-test was used in groups comparison with a probability of <0.05 considered to be statistically significant. The correlation coefficient (r) was calculated by regression analysis. For differences related to the presence or absence of thrombosis, abortion and clinical activity the Fisher's exact test was used.

Results

Eighty patients with connective tissue diseases were studied (Table 1). A history of arterial or venous thrombosis was present in 12 patients (14%). Fourteen women (22%) had a history of recurrent abortions and/or fetal loss. Obstetric complications

were significantly higher in SLE patients ($p < 0.02$). Antiphospholipid antibodies, considered positive LA and/or ACA, were detected in 38 out of 80 patients (47.5%). Positive LA was present in 29 patients (36.2%) and ACA in 18 (22.5%). Antiphospholipid antibodies significantly correlated with a history of thrombosis and abortions ($p < 0.05$). They were also more frequently present ($p = 0.009$) in patients during the active phase of the disease (23%) with respect to patients with inactive disease (77%).

Table 2 summarizes the results of fibrinolysis parameters before and after venous occlusion in the group of patients as compared to controls. Before occlusion t-PA Ag and PAI-1 concentrations were significantly higher in the group of patients ($p < 0.0001$). Fibrinogen levels were also elevated ($p = 0.002$). No significant differences were observed in any of the other parameters analyzed before venous occlusion.

The fibrinolytic activity after venous occlusion, assessed on fibrin plates, and the fibrinolytic response, were significantly lower in patients as compared to controls ($p = 0.003$ and $p = 0.002$ respectively), whereas t-PA activity and t-PA capacity were similar between groups. The t-PA antigen after occlusion was significantly higher in the patient group ($p = 0.03$), but no

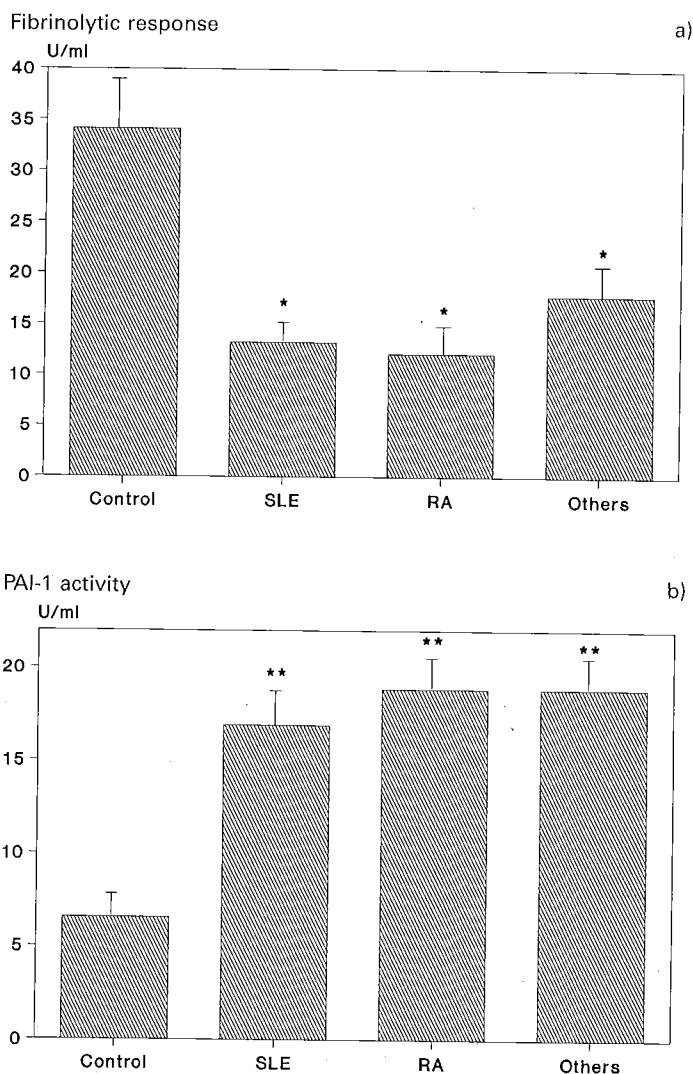


Fig. 2 a) t-PA capacity (calculated as the difference between t-PA activity levels in postocclusion and preocclusion plasma samples) and b) t-PA release (difference between t-PA Ag postocclusion and preocclusion) in patients and controls. Mean \pm SEM is reported. Abbreviations are as in Fig. 1

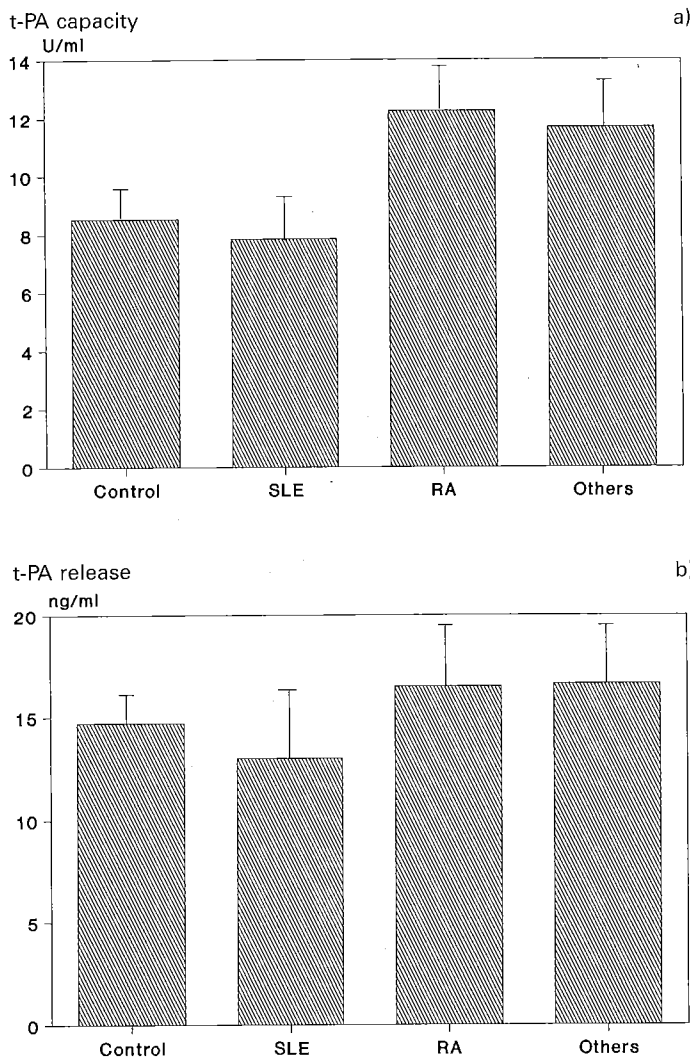


Fig. 1 a) Fibrinolytic response (mean \pm SEM values of the difference between EFA postocclusion and preocclusion) and b) plasma PAI-1 activity before occlusion in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other non-SLE disorders.

* $p < 0.01$ and ** $p < 0.001$ as compared to the control group

differences for t-PA release were observed in patients and controls. Interestingly, higher residual PAI-1 activity after venous occlusion was observed in the group of patients ($p = 0.001$).

Fig. 1 shows the fibrinolytic response and PAI-1 levels in the control group and in patients with SLE, rheumatoid arthritis and other diseases. Low fibrinolytic response was observed in all patient groups as compared to controls ($p < 0.01$). The plasma activity of PAI-1 before occlusion was significantly increased in the different groups with respect to the control group ($p < 0.005$). High PAI-1 activity levels (>12 U/ml) were observed in 52% of SLE patients, 76% of patients diagnosed of RA and in 73% of patients in the miscellaneous group.

Fig. 2 shows the t-PA capacity and t-PA release in the control group and in patients with SLE, RA and other diseases. No significant differences in either parameter were observed in patients and controls, but the groups of RA and other diseases showed a slight increase of t-PA capacity and t-PA release.

A negative correlation between PAI-1 and the fibrinolytic response ($r = -0.35$, $p < 0.002$) was observed. No other correlation between any of the various fibrinolysis parameters analyzed could be demonstrated.

Neither the presence or absence of thrombosis nor the activity of the disease had consequences on the measurement of the different fibrinolysis parameters, although the PAI-1 activity was slightly elevated in those patients with a history of thrombosis (19.56 ± 11.42 vs 16.91 ± 10.08 U/ml) without statistical differences.

Only the t-PA release was found to be significantly lower ($p < 0.05$) in women with history of abortions (mean 9.24 ± 5.34 ng/ml) as compared to those without obstetric complications (mean 17.51 ± 14.73 ng/ml). Likewise, the PAI-1 activity showed a tendency to increase in women with obstetric complications (19.03 ± 9.54 vs 16.88 ± 10.53 U/ml). Fibrinogen was significantly increased ($p = 0.0006$) in patients with positive APA (467.2 ± 107.2 mg/dl) with respect to those with negative APA (374.1 ± 98.8 mg/dl). There was no correlation between the presence of APA and the other fibrinolysis parameters analyzed.

Discussion

This study shows a significant increase of APA and an impairment of fibrinolysis in SLE as well as in other connective tissue disorders, mainly related to disturbances in the t-PA/PAI-1 system. However, no correlation between the presence of antiphospholipid antibodies and fibrinolysis abnormalities could be demonstrated.

We found a large number of patients with positive APA in a similar percentage to that reported in the literature (1, 2). An unexpected finding was that LA was detected more frequently than ACA, but no conclusion can be drawn from our results. A good positive correlation between APA and a history of thrombosis or abortions was observed. Antiphospholipid antibodies are well known risk factors for thrombosis and obstetric complications in patients with SLE and other closely related disorders (19). Both arterial and venous thrombosis have been associated with the presence of such antibodies, although current knowledge points out to the possibility of a multifactorial origin, derived from an imbalance in the procoagulant and anticoagulant systems as well as from impaired fibrinolysis (20, 21).

Previous reports have already shown deficiencies in plasminogen activators or abnormalities in the t-PA/PAI-1 system in patients with SLE (8–10, 22, 23), but few reports have been published on the fibrinolytic potential assessed before and after occlusion (24), and no reliable information is known about the fibrinolytic potential in other non-SLE disorders associated with antiphospholipid antibodies (25, 26).

In our study the overall fibrinolytic activity as well as the t-PA activity before occlusion did not differ significantly between patients and controls. However, a marked increase in PAI-1 and t-PA Ag levels was observed in the group of patients. Several authors have found an increase of PAI-1 levels in SLE patients (8, 10, 22, 23), but few studies have demonstrated similar findings in non-SLE related disorders (27). Such increase might be explained by release of PAI-1 as a result of immunologically induced endothelial cell damage (28, 29). Although an acute phase reactant behavior cannot be ruled out, the lack of correlation between PAI-1 and fibrinogen levels allows us to exclude this possibility. The high resting t-PA Ag levels found in the patient group could also indicate the t-PA/PAI-1 complex formation. Recently, Violi et al. (10) and Ruiz Argüelles et al. (23) have also reported similar findings in SLE patients. Others have, however, found normal or reduced t-PA Ag levels (30, 31).

A significant reduction in the fibrinolytic response to venous occlusion was observed in the total group of patients and in each of the different groups. Previous reports have also found similar results in SLE patients (7, 22, 24), but there are no data

concerning reumatoid arthritis and other connective tissue diseases. However, t-PA capacity and release were similar in patients and controls. Since a negative correlation between PAI-1 and the fibrinolytic response was observed, it can be assumed that the reduced fibrinolytic activity is mainly due to raised PAI-1 levels rather than to reduced t-PA.

No correlation between the impairment in the fibrinolysis parameters and the activity of the disease could be demonstrated, as it has already been previously reported (10, 32). Higher PAI-1 levels were found in patients with thrombosis, although no significant differences were found. This could be due to the fact that only 12 out of 80 patients developed thrombotic complications and thus no definitive conclusions can be drawn. It is interesting to point out that the observed changes are quite similar to those reported in patients with idiopathic deep vein thrombosis, indicating that the abnormal thrombogenesis observed in patients with connective tissue diseases could in part be due to an impairment in the fibrinolysis mechanisms (33). In addition, high residual plasminogen activator inhibitor activity was found in the patient group. Nguyen et al. (34) have suggested that this parameter would be useful to define a bad fibrinolytic response. They observed hypofibrinolysis, defined by the inability of released t-PA to overcome PAI-1 inhibitor potential, in a high proportion of patients with deep vein thrombosis.

A significant reduction in the t-PA release and a tendency to increased PAI-1 concentrations were found in women with clinical history of abortions, indicating that the fibrinolytic system is deeply affected in these patients. Violi et al. (10) have also found high PAI-1 levels in patients with abortions which they associate with the presence of lupus anticoagulant. Nevertheless, more studies are needed to elucidate the role of the fibrinolytic system and the possible link between the increase in plasma PAI-1 activity and the occurrence of abortions.

Finally, the observed changes in the fibrinolysis parameters were not related to the presence of antiphospholipid antibodies, which agrees with recent reported data (24). Controversy still exists in the literature as to the possible relationship between APA and impaired fibrinolysis due to changes in the t-PA/PAI-1 system (7, 10, 23, 29, 31, 32). In our study such a correlation could not be demonstrated. Whereas the occurrence of thrombosis and abortions seems to be linked to the presence of antiphospholipid antibodies, we were not able to show a significant correlation between the increase of PAI-1 and the presence of lupus anticoagulant and/or ACA.

In conclusion, this study shows a significant impairment of fibrinolysis in patients with connective tissue disorders. Reduced fibrinolysis, mainly related to high PAI-1 levels, may play a significant pathogenetic role in these diseases.

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A new successful strategy

This booklet is a valuable summary of the latest findings in an increasingly important medical topic - blood saving in cardiac surgery. The authors who are members of the Society for Heart Transplantation present clinical experiences and research results in a concise and informative way. Current blood saving strategies in surgery, posttransfusion infections, autologous blood transfusions are reviewed and their risk-benefit ratio is examined.

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