

LETTERS TO THE EDITOR

von Willebrand factor and vascular injury in rheumatoid arthritis

In their interesting paper Farrel *et al* showed that joint exercise induced an increased plasma concentration of the von Willebrand factor (vWF) in patients with rheumatoid arthritis (RA).¹

The authors suggested that the observed altered concentrations should be best explained by synovial endothelial release during hypoxic reperfusion injury. Previous reports published by us and others have shown increased concentration of anti-cardiolipin antibodies (aCL) in both adult and juvenile patients with RA.²⁻⁴ Anti-phospholipid antibodies (for example, anti-cardiolipin) in RA are associated with different vascular complications, including arterial and venous thrombosis and generally vasculitis.^{3,4}

In a recent study we included 54 patients with RA who satisfied the 1987 American Rheumatism Association Criteria and were enrolled from our Extra-articular Involvement RA Clinic (EIRAC). From 1991 EIRAC has evaluated (as a secondary referral centre) patients mainly from the Genoa area affected by frequent RA complications, such as, Sjögren's syndrome, vasculitis and hypertension. The patients with RA who were included in this study, were grouped as 'aCL positive' (n = 18) and 'aCL negative' (n = 36) with regard to the aCL positivity.

The laboratory findings included the vWF and the vitamin-K dependent anticoagulant proteins: protein C and its cofactor protein S, as well as antinuclear antibodies (ANA), antibodies to Scl-70 (anti Scl-70), double stranded DNA (anti ds-DNA) and extractable nuclear antibodies (ENA), to investigate the possible relationship among these parameters, recent episodes of thrombosis (lasting less than six months) and the aCL positivity.

vWF is reportedly increased in connective tissue disorders characterised by vascular disease and provides a selective marker of altered endothelial cell function as correlate of disease.⁵

In the present study the aCL positive patients with RA were confirmed to be affected by a significantly higher rate (n = 7/18; 39%) of recent venous (n = 6/7, deep vein thrombosis; 86%) and arterial (n = 1/7, ophthalmic artery thrombosis; 14%) thrombosis (total = 39% v 14%, aCL negative and versus 9%, controls (osteoarthritis); p < 0.05). Conversely, a significant increase of the vWF was found in aCL positive versus aCL negative RA patients (p < 0.001), as well as in aCL positive RA patients versus controls (p < 0.001) (table).

A significant increase of the vWF levels was observed in aCL positive RA patients with a history of thrombosis compared with the aCL positive patients with a negative history of thrombosis and with the controls (p < 0.05) (table).

On the other hand, 67% of the aCL positive RA patients were found positive for

Comparison of serological and clinical findings in aCL positive and negative RA patients

	aCL positive RA patients (n = 18; 33%)	aCL negative RA patients (n = 36; 67%)	Controls (Osteoarthritis) (n = 45)
Men/Women	4/14	7/29	9/36
Age (years)	52.3 (3.6)	55.5 (3.9)	50.2 (4.6)
vWF (% of normal)	163 (50)**	107 (32)	98 (42)
Protein S (% of normal)	72 (20)**	95 (16)	108 (23)
Protein C (% of normal)	105 (18)	108 (10)	103 (24)
RF-IgM positive (no of patients)	17 (94%)	33 (91%)	0
ANA positive (no of patients)	12/18 (67%)	18/36 (50%)	
SSA positive (no of patients)	9/18 (50%)	14/36 (39%)	
History of thrombosis (no of patients)	7/18 (39%)*	5/36 (14%)	4/45 (9%)

History of Thrombosis (+ or -)	aCL positive		aCL negative		Controls (Osteoarthritis)	
	+	-	+	-	+	-
No of patients	7/18 (39%)	11/18	5/36 (14%)	31/36	4/45 (9%)	41/45
vWF (% of normal)	210 (16)*	136 (37)	173 (20)	93 (21)	162 (24)	77 (35)
Protein S (% of normal)	63 (14)*	70 (24)	91 (11)	98 (18)	96 (34)	110 (24)
Protein C (% of normal)	110 (8)	101 (10)	107 (13)	102 (9)	109 (27)	104 (21)

§Patients labelled as 'aCL positive' showed concentration of antibodies of more than 5SD over the mean values obtained from controls. All values are expressed as mean (SD). vWF = von Willebrand Factor; RF-IgM = Rheumatoid Factor-IgM; ANA = Antinuclear antibodies; SSA = anti-SSA antibodies.

*p < 0.05; **p < 0.001 (Student's t test and the Fisher's exact test). The detection of the aCL was performed by an enzyme linked immunosorbent assay (ELISA) as previously described.¹ vWF levels were assayed by a standard ELISA technique and the concentrations were expressed as the percentage of values of the pooled normal standard serum.

ANA at low titre and with a speckled immunofluorescence pattern (versus 50% aCL negative RA patients). No positivity was found for antibodies to ENA, ds-DNA and Scl-70; only the SSA subset was found positive in patients with associated Sjögren's syndrome (50% versus 39% aCL negative RA patients) (see table).

At the same time, a significant decrease of total protein S levels was observed in the aCL positive RA patients versus aCL negative RA patients and controls (p < 0.001); protein C levels were found almost similar in all groups (table).

As a result of the frequent extra-articular manifestations observed in RA patients with severe involvement, the identification of a subset of patients with elevated concentrations of aCL, increased frequency of thrombosis and related abnormalities of the vWF levels, may be of clinical interest.

The evidence reported by Farrel that vWF is increased in RA patients after joint exercise, probably released from synovial endothelial cells as a result of the initial hypoxia and subsequent oxidant events, is a further interesting possibility.¹

In addition, we suggest that in analysing RA patients with vascular complications and increased plasma concentrations of the vWF, the presence of the anticardiolipin antibodies should be investigated and the patients together with the steroidal and immunosuppressive therapy should receive long term anticoagulant treatment, if aCL concentrations are repeatedly found.⁶

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1 Farrel A J, Williams R B, Stevens C R, Lawrie A S, Cox N L, Blake D R. Exercise induced release of von Willebrand factor: evidence for hypoxic reperfusion microvascular injury in rheumatoid arthritis. *Ann Rheum Dis* 1992; 51: 1117-22.

2 Seriole B, Cutolo M, Fasciolo D, Accardo S. Anticardiolipin antibodies in rheumatoid arthritis. *Ann Rheum Dis* 1991; 50: 1100.

3 Caporali R, Ravelli A, De Gennaro F, Neirotti G, Montecucco C, Martini A. Prevalence of anticardiolipin antibodies in juvenile chronic arthritis. *Ann Rheum Dis* 1991; 50: 599-601.

4 Hughes G R V. The antiphospholipid syndrome: ten years on. *Lancet* 1993; 342: 341-4.

5 Pearson J. Markers of endothelial perturbation and damage. *Br J Rheum* 1993; 29: 67-71.

6 Loizou S, McCrea J D, Derve G G M, *et al*. Measurement of anticardiolipin antibodies by an enzyme-linked immunoadsorbent assay (ELISA): standardization and quantification of results. *Clin Exp Immunol* 1985; 62: 738-45.

7 Blann A D, Hopkins J, Winkles J, Wainwright A C. Plasma and serum von Willebrand factor concentrations in connective tissue disorders. *Ann Clin Biochem* 1992; 29: 67-71.

8 Derkx R H W M, de Groot Ph G, Kater L, Nieuwenhuis H K. Patients with antiphospholipid antibodies and venous thrombosis should receive long term anticoagulant treatment. *Ann Rheum Dis* 1993; 52: 689-92.

Successful treatment of right atrial thrombus in a patient with Behçet's disease

Behçet's disease, a syndrome of recurrent oral and genital ulceration and relapsing uveitis,¹ is frequently complicated by vasculitis and venous system involvement which may lead to inferior vena caval (IVC)² obstruction and Budd-Chiari syndrome.³

We report a case of Behçet's disease referred for investigation of a right atrial mass associated with IVC obstruction and Budd-Chiari syndrome successfully treated with anticoagulation and immunosuppressive therapy.

A 32 year old male car factory worker presented with an 18 months history of general malaise, weight loss, recurrent skin lesions and abdominal swelling. Tender hepatomegaly was detected and liver biopsy showed severe centrilobular venous congestion. Subsequent 2D-echocardiography revealed a right atrial mass. Following referral to our department cachexia and low grade fever were observed and he had widespread ulceration of the oral mucosa, nodular and pustular skin lesions (some of which were ulcerating), and pathergy phenomenon