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 3] 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 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).

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 S (% 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%)

Analysis of the patients with history of thrombosis:

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.[3 6] 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.

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 Farrell 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.[7]

BRUNO SERIOLO
SILVANO ACCARDO
MAURIZIO CUTOLO
Division of Rheumatology, Department of Internal Medicine, University of Genova, Italy

Correspondence to: Dr B Seriolo, Cattedra di Reumatologia, DI M I, Università di Genova, Viale Benedetto XV, No 6 16132 Genova, Italy.

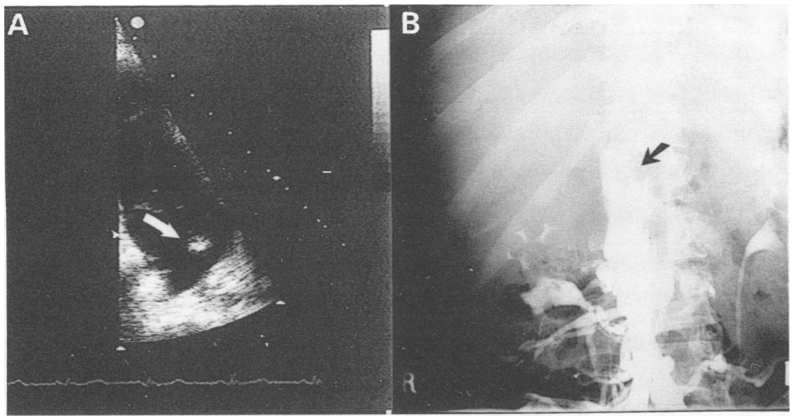
1 Farrell A J, Williams R B, Stevens C R, Lawrie A S, Cox N L, Blake D R. Exercise induced release of von Willebrand factor: evidence for hypoxic reperfusion microvascular injury in rheumatoid arthritis. *Ann Rheum Dis* 1992; **51:** 1117–22.
2 Seriolo B, Cutolo M, Fasciolo D, Accardo S. Anticardiolipin 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 Derkens 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



A: Pre-treatment 2D echocardiogram showing right atrial thrombus (arrow); B: IVC angiogram demonstrating the level of obstruction (arrow).

(sterile skin pustules at sites of venepuncture) was noticed. There was evidence of penile and scrotal scarring. Prominent distended veins over the anterior abdominal wall and lower chest were present.

His chest radiograph was normal and repeat 2D-echocardiogram showed a sessile 1 cm diameter mass within the right atrium, lying above the inflow of the inferior vena cava (IVC) and attached to the posterior wall (fig A). A venogram revealed occlusion of the IVC with extensive collateral circulation (fig B) and abdominal CT showed patchy inhomogeneity of the liver with enlargement of the caudate lobe and virtually no visualisation of the hepatic veins.

An elevated serum factor VIII RAg (510 IU/dl) and weakly positive neutrophil cytoplasmic (perinuclear pattern) antibodies were observed.

Behçet's disease was diagnosed, complicated by Budd-Chiari syndrome and right atrial thrombus.

He was treated with warfarin, prednisolone (40 mg/day, reduced over 12 months to 15 mg/day) and azathioprine (125 mg/day). On review after three months of treatment there was no hepatomegaly and we did not observe any distended abdominal veins. 2D-echocardiography showed reduction in the size of the right atrial mass. The level of factor VIII RAg diminished (320 IU/dl) and neutrophil cytoplasmic antibodies were not detectable.

At six months follow up, bilateral cataracts and mild retinal vasculitis developed. The first improved after reducing his steroids and the latter has not advanced when reviewed 18 months later. Transoesophageal echocardiography at this stage showed no evidence of the thrombus in the right atrium.

Mass in the right atrium may be due to a primary or metastatic tumour, endocarditis involving the right side of the heart, or thrombus formation.[4-6]

Thrombus within the right ventricle was first described at necropsy in a patient with Behçet's disease who presented with haemoptysis and pulmonary lesions.[7] In two other reports it was observed either at necropsy or after surgery.[3 8] In our case this rare complication of Behçet's disease was diagnosed by 2D-echocardiography and successfully treated with a combination of anticoagulation and immunosuppressive therapy.

This report confirms that right atrial thrombus occurs in association with Behçet's syndrome and can be successfully treated by medical means.

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ISMAIL F ISLIM
MARTIN D GILL
DEVA SITUNAYAKE
ROBERT D S WATSON
Cardiology and Rheumatology Departments
Dudley Road Hospital
Birmingham
United Kingdom

Correspondence to: Dr Ismail F Islim, Cardiology Department, Dudley Road Hospital, Birmingham B18 7QH, United Kingdom.

1 Behçet's H. Uber rezidivierende Aphthose, durch ein virus versuchate Geshwure am Mund. Am Auge und an den Gentalien. *Derm Wschr* 1937; **105:** 1152.
2 Kansu E, Ozer F L, Akalin E, *et al.* Behçet's syndrome with obstruction of the venae cavae. A report of seven cases. *Quarterly J Med* 1972; **41:** 131–68.
3 McDonald G S A, Gad Al-Rab. Behçet's disease with endocarditis and the Budd-Chiari syndrome. *J Clin Path* 1980; **33:** 660–9.
4 Kapoor A S. Clinical manifestations of neoplasia of the heart. In: Kapoor A S, ed. Cancer and the heart. New York: Springer-Verlag, 1986; 21–5.
5 Schoen F J, Berger B M, Guerina N G. Cardiac effects of non-cardiac neoplasia. *Cardiol Clin* 1984; **2:** 657.
6 Rajpal R S, Leibsohn S A, Lickweg W G, *et al.* Infected left atrial myxoma with bacteraemia simulating infective endocarditis. *Arch Intern Med* 1979; **139:** 1176.
7 Davies J D. Behçet's disease with haemoptysis and pulmonary lesions. *J Pathol* 1973; **109:** 351–6.
8 Candan I, Erol C, Sonel A, *et al.* Behçet's disease, cardiac and pulmonary involvement. *Europ H J* 1986; **7:** 999–1002.

Dyslipoproteinaemia in a subset of patients with rheumatoid arthritis

It has been clearly established that patients with rheumatoid arthritis (RA) have an accelerated mortality in comparison with the general population.[1-3] The primary cause of death for patients with RA is cardiovascular disease. Although one older study suggested otherwise,[4] several more recent series have concluded that the incidence of atherosclerotic cardiovascular disease (ASCVD) in patients with RA may exceed that of controls.[2 3] Risk factors for the development of ASCVD include male sex, family history, cigarette smoking, hypertension, diabetes mellitus, and dyslipoproteinaemia.[5] Lipoprotein profiles that predispose to the development of ASCVD include high levels of total cholesterol (TC) or low density lipoprotein cholesterol (LDL-C), and low levels of high density lipoprotein cholesterol (HDL-C). In several series, patients with RA have been shown to have serum cholesterol concentrations significantly lower than controls.[6 7] However, such studies have usually included a significant proportion of persons with few risk factors for ASCVD, for example young women. We have investigated the serum lipoprotein profile of a group of older males with RA.

Sixty male patients with RA followed at the Dallas Department of Veterans Affairs Medical Center arthritis clinic were evaluated. Patients who were receiving treatment with lipid-lowering agents, as well as patients with diabetes mellitus or thyroid disease, were excluded from analysis. The average mean (SD) age of the patients was 62 (11) years. All patients were receiving treatment with disease modifying antirheumatic drugs (methotrexate 23, sulfasalazine 13, injectable gold 12, D-penicillamine 9, auranofin 1, azathioprine 1, cyclophosphamide 1). Thirty three patients (55%) were receiving therapy with corticosteroids [mean (SD) dose for those receiving prednisone: 6·8 (3·4) mg/day; median dose 5 mg/day (range 4–20)]. Twenty two patients were being treated with antihypertensives, including four patients treated with a β-blocker and five with a diuretic. Fasting cholesterol, HDL-C, and triglycerides (TG) were determined enzymatically. LDL-C was estimated using the formula LDL-C= TC – (HDL-C + TG/5).

Lipoprotein profiles are shown in the table. Although mean values are within normal range, a substantial number of patients have concentrations of lipoproteins considered to be a risk for the development of ASCVD. Thus 11/60 (18%) patients would be considered at 'high risk' of developing ASCVD on the basis of TC or LDL-C, according to National Cholesterol Education Programs recommendations (TC ≥ 6·21 mmol/L [240 mg/dL]; LDL-C ≥ 4·14 mmol/L [160 mg/dL]).[5] Furthermore, it has been established that persons within this particular population (that is, male veterans) often possess multiple additional risk factors for ASCVD.[8] Therefore, 8/60 (13%) additional patients with 'borderline risk' levels of TC and LDL-C (TC ≥ 5·17 mmol/L [200 mg/dL] LDL-C ≥ 3·36 mmol/L [130 mg/dL]) would be considered to have significant dyslipoproteinaemia. Recently, the important role of decreased levels of HDL-C as a risk factor for ASCVD has been increasingly appreciated.[9] Of note, 30/60 (50%) of the patients had depressed serum HDL-C (≤0·91 mmol/L [35 mg/dL]), of whom 12/60 (20%) had concentrations ≤0·78 mmol/L (30 mg/dL). In total, 41/60 patients (68%) had serum concentrations of TC, LDL-C, or HDL-C that would be considered risk factors for the development of ASCVD. In contrast to other studies,[9] there was no correlation between the use of corticosteroids and serum concentrations of TC, TG, HDL-C, or LDL-C. A similar lack of correlation has been noted in some studies,[7] and may relate to the intrinsic propensity toward dyslipoproteinaemia in the specific populations analysed.

It is accepted that the mortality of patients with RA is accelerated and that ASCVD is an important contributory factor. It has been