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). 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. Anti-phospholipid antibodies (for example, anti-cardiolipin) in RA are associated with various vascular complications, including arterial and venous thrombosis and generally vasculitis.

In a recent study we included 54 patients with RA who satisfied the 1987 American Rheumatism Association Criteria and were enrolled from our Extra-arterial 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 anti-nuclear antibodies (ANA), antibodies to ScI-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.

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% + 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 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 ScI-70; only the SSA sub-set 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-arterial 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 oxidative events, is a further interesting possibility.

In addition, we suggest that in analysing RA patients with vascular complications and increased plasma concentrations of the vWF, the presence of the anti-cardiolipin 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.

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Successful treatment of right atrial thrombus in a patient with Behcet’s disease

Behcet’s disease, a syndrome of recurrent oral and genital ulceration and relapsing uveitis is frequently complicated by vasculitis and venous system involvement which may lead to inferior vena cava (IVC) obstruction and Budd-Chiari syndrome.

We report a case of Behcet’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 24 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 central portal venous congestion. Subsequent 2D-echocardiography revealed a right atrial mass. Following referral to our department cieacia and low grade fever were observed and he had widespread ulceration of the oral mucosa, nodular and purpuric skin lesions (some of which were ulcerating), and pathergy phenomenon
(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-echocardiography 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.

Thrombus within the right ventricle was first described at necropsy in a patient with Behçet's disease who presented with haemoptysis and pulmonary lesions.¹ In two other reports it was observed either at necropsy or after surgery.² 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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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 ² The primary cause of death for patients with RA is cardiovascular disease. Although one older study suggested otherwise,³ several more recent series have concluded that the incidence of athero- sclerotic cardiovascular disease (ASCVD) in patients with RA may exceed that of controls.⁴ Risk factors for the development of ASCVD include male sex, family history, cigarette smoking, hypertension, diabetes mellitus, and dyslipoproteinemia.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 high 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.² ⁶ 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, p-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 anti-hypertensives, 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" (LDL-C > 130 mg/dL) and 41/60 (68%) at "borderline risk" (LDL-C > 110 mg/dL) to developing ASCVD. The latter group was divided into subgroups: a) patients with high TG (TG > 200 mg/dL); b) patients with high TC; c) patients with high LDL-C. In the first group 5/13 (39%) patients had high LDL-C ( > 130 mg/dL) and in the second group 8/17 (47%) had high LDL-C ( > 130 mg/dL) and in the third group 30/41 (73%) had high LDL-C ( > 130 mg/dL). In contrast to the other two groups there was no correlation between the use of corticosteroids and serum concentrations of TC, LDL-C, or HDL-C; this would be considered risk factors for the development of ASCVD. In contrast to other studies there was no correlation between the use of corticosteroids and serum concentrations of TC, LDL-C, or HDL-C that was considered risk factors for the development of ASCVD. In contrast to other studies there was no correlation between the use of corticosteroids and serum concentrations of TC, LDL-C, or HDL-C that was considered risk factors for the development of ASCVD. In contrast to other studies there was no correlation between the use of corticosteroids and serum concentrations of TC, LDL-C, or HDL-C that was considered risk factors for the development of ASCVD. In contrast to other studies there was no correlation between the use of corticosteroids and serum concentrations of TC, LDL-C, or HDL-C that was considered risk factors for the development of ASCVD. In contrast to other studies there was no correlation between the use of corticosteroids and serum concentrations of TC, LDL-C, or HDL-C that was considered risk factors for the development of ASCVD. In contrast to other studies there was no correlation between the use of corticosteroids and serum concentrations of TC, LDL-C, or HDL-C that was considered risk factors for the development of ASCVD. In contrast to other studies there was no correlation between the use of corticosteroids and serum concentrations of TC, LDL-C, or HDL-C that was considered risk factors for the development of ASCVD.