Inflammation in Patients with Lupus Anticoagulant and Implications for Thrombosis

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ABSTRACT. ***Objective.*** The underlying mechanism of the prothrombotic state associated with the lupus anticoagulant (LAC) has not been fully elucidated. Evidence suggests involvement of inflammation in arterial and venous thrombosis, and it may be hypothesized that subclinical inflammation aggravates the tendency to thrombosis in patients with LAC.

Methods. Levels of high sensitivity C-reactive protein (hs-CRP), fibrinogen, and factor VIII (VIII) were measured in 38 patients with LAC and a history of thrombosis, 27 with LAC and no history of thrombosis, and 33 healthy controls.

Results. Hs-CRP, fibrinogen, and factor VIII levels were significantly higher in patients with LAC with thrombosis (hs-CRP median = 0.3 mg/dl, interquartile range, IQR, 0.11–0.62, $p < 0.001$ vs controls; fibrinogen mean = 395 ± 90 SD mg/dl, $p < 0.001$; factor VIII mean = 181 ± 50%, $p = 0.005$) as well as in those without thrombosis (median = 0.21, IQR 0.10–0.12, $p < 0.001$; mean = 378 ± 91, $p = 0.003$; mean = 179 ± 39, $p = 0.015$) compared to controls (median = 0.07, IQR 0.03–0.12; mean = 308 ± 48; mean = 137 ± 39). After adjustment for age, body mass index, smoking status, and blood group (only for factor VIII) the differences between LAC groups and controls remained significant, except for the comparison of fibrinogen between patients without thrombosis and controls. The association between LAC and markers of inflammation was confirmed using linear regression analysis. Markers of systemic inflammation did not differentiate between LAC patients with and without thrombosis ($p = 0.829$ for hs-CRP, $p = 0.649$ for fibrinogen, $p = 0.996$ for factor VIII).

Conclusion. Our results show that LAC is associated with an inflammatory state. However, there was no evidence for an association between inflammatory markers and thromboembolism in patients with LAC. (J Rheumatol 2005;32:462–8)

Key Indexing Terms:
LUPUS ANTICOAGULANT AUTOIMMUNE DISEASE THROMBOSIS
INFLAMMATION MARKERS OF INFLAMMATION

The lupus anticoagulant (LAC) belongs to the group of antiphospholipid antibodies and prolongs *in vitro* phospholipid-dependent coagulation tests[1], but is associated with venous and arterial thrombosis and fetal loss *in vivo*[2,3]. Thromboembolic events are reported in about one-third of antiphospholipid antibody-positive patients[4]. Although LAC is a strong risk factor for thrombosis, a subgroup of LAC patients remains unaffected. Various theories on the pathogenesis of thrombosis in LAC have been suggested, but the clinically relevant procoagulatory mechanism has not been elucidated so far.

LAC comprises a heterogeneous group of autoantibodies directed against epitopes located either on phospholipids or on proteins serving as cofactors at the binding site of negatively charged surfaces. A great variety of antibodies directed against phospholipid-dependent proteins have been identified, whose target epitopes are found on beta-2 glycoprotein I ($ß_2$-GPI)[5], prothrombin[6], protein C[7], protein S[8], and annexin V[9]. Since the influence of these autoantibodies on thrombosis remains controversial and LAC does not always provoke thrombosis in all patients, it might be assumed that other pathomechanisms contribute to the procoagulatory state in patients with LAC.

Recently, the role of inflammatory processes in thrombosis has been under intensive investigation. Data on experimental and clinical studies provide evidence for a linkage between inflammation and coagulation and support the idea that inflammation might be involved in the development of

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thrombosis. It has been shown that inflammation induces the expression of tissue factor, an integral part of the initiation of coagulation[10-12]. The presence of inflammation reduces the fibrinolytic activity through upregulation of the production of plasminogen activator inhibitor (PAI)[13]. Further, the anticoagulant effect of the protein C pathway is impaired due to downregulation of thrombomodulin[14-16] and a decrease of protein S[17].

We investigated whether LAC influences inflammatory markers and whether inflammatory markers have an influence on the development of thrombosis in patients with LAC.

MATERIALS AND METHODS

Between 1976 and 2001, 110 adult patients were given the diagnosis of a persistent LAC at our outpatient department. These patients were invited to a followup investigation and were asked to participate in this study, which was approved by the local Ethics Committee. Eighty-one patients with previously detected LAC accepted and were enrolled in the study between May 2001 and May 2002. After written informed consent had been obtained, patients' medical history was recorded using a standardized questionnaire and blood samples were drawn. Blood collection was performed at least 3 months after a thrombotic event. At the time of inclusion no patient had an overt infection. The diagnosis of persistent LAC was established when LAC was detected according to the International Society on Thrombosis and Haemostasis (ISTH) criteria at least twice in an interval of at least 3 months[18]. Sixteen patients were excluded because diagnostic criteria for LAC were not fulfilled. A total of 65 patients with persistent LAC were included in the study, 38 with a history of an objectively confirmed venous and/or arterial thrombotic event. The diagnostic methods included ultra or duplex sonography or phlebography for venous thrombosis, computerized tomography, or ventilation/perfusion scan or lung scan for pulmonary embolism and adequate objective methods for arterial thrombosis. Thirty-three healthy individuals served as controls.

Systemic lupus erythematosus (SLE) was diagnosed according to American Rheumatism Association (ARA) criteria[19]. Patients characterized by antinuclear antibodies and disease symptoms related to one organ system were described as having incomplete SLE[20].

Laboratory methods. LAC testing was performed within 3 h of blood sampling. Diagnosis of the LAC was made according to the revised criteria proposed by the Subcommittee for Standardization of LAC[18] by using 2 different screening tests (activated partial thromboplastin time and dilute Russell's viper venom time) and a confirmatory test as described[21].

High sensitivity C-reactive protein (hs-CRP) was measured from freshly thawed citrate-plasma samples with a nephelometric assay on a Behring Nephelometer II (Dade-Behring, Delaware, MD, USA). The day-to-day imprecision of the method was < 5% for hs-CRP levels between 0.03 and 24 mg/dl. Fibrinogen (normal range 180–390 mg/dl; STA fibrinogen, Diagnostica Stago, Asnieres, France) was measured according to Clauss on a STA Compact Analyser. Factor VIII activity (normal range 60–230%) was determined as described[22], using a Sysmex CA 7000 analyzer (TOA Medical Electronics, Kobe, Japan). Established risk factors for venous thrombosis (factor V:R506Q mutation, G20210A prothrombin variation, hyperhomocysteinemia, or a deficiency of antithrombin, protein C and protein S) were diagnosed as described[23].

Anticardiolipin antibodies (aCL) were measured by a commercial indirect noncompetitive enzyme immunoassay [Synelisa, Pharmacia & Upjohn, Friburg, Germany; normal range ≤ 15 IgG phospholipid units/ml (GPL/ml) for aCL IgG and ≤ 15 IgM phospholipid units (MPL/ml) for aCL IgM][24].

Statistical analysis. Data are expressed as mean ± standard deviation or as median and interquartile range (IQR). The chi-square test was used to compare categorical data between groups. As the distribution of CRP was skewed, logarithmic transformation was performed to allow parametric tests. To test for differences of inflammatory markers (hs-CRP, fibrinogen, factor VIII) between groups, analysis of variance with the factor group (3 levels) only and additionally with smoking status (2 levels: smokers/nonsmokers) and the covariates age and body mass index (BMI) were calculated and *post hoc* tests according to Tukey were performed. In the analysis of factor VIII the blood group was additionally entered as covariate. A multivariable linear regression analysis including the parameters LAC status, aCL IgM and IgG above upper limit of normal was used to investigate the association of these parameters with CRP, fibrinogen, and factor VIII, respectively. A multivariable binary logistic regression analysis including the parameters CRP, fibrinogen, factor VIII, aCL IgM and IgG above upper limit of normal, age, sex, and a dummy variable (2 levels: negative in case of absence and positive in case of presence of at least one of the following thrombosis risk factors: factor V:R506Q mutation, G20210A prothrombin variation, hyperhomocysteinemia, or a deficiency of antithrombin) was applied to calculate the thrombosis risk. The Spearman rank correlation coefficient was used to assess the relationship between markers of inflammation, age, and BMI. A 2-sided p value < 0.05 was considered statistically significant. Calculations were performed using SAS software system V8.02 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 38 patients with LAC with (34 women, 4 men) and 27 without (19 women, 8 men) a history of thrombosis as well as 33 healthy controls (25 women, 8 men) were included in the study. The patients' characteristics including data on aCL IgG and IgM levels are summarized in Table 1. The median age was higher among patients without thrombosis than among those with thrombosis (p = 0.009). LAC groups were comparable with respect to the BMI, the frequency of blood group O, and the male to female ratio. SLE and incomplete SLE were present in 7 and 6 patients with thrombosis and in 3 and 6 patients without thrombosis, respectively. In addition, one patient without thrombosis had rheumatoid arthritis and one patient with thrombosis had an immune phenomenon characterized by autoimmune hepatitis, autoimmune thyroiditis, vasculitis, and Sjögren's syndrome. Immunosuppressive treatment was administered to 5 patients with thrombosis (corticosteroids in 3, azathioprine in one, corticosteroids combined with azathioprine in one) and 3 patients without thrombosis (all corticosteroids). At study entry the LAC was known for a median of 2.2 years in patients with thrombosis and 1.9 years in patients without thrombosis.

Of the 38 LAC-positive patients with thrombosis, 26 had a history of only venous thromboembolism, 4 had venous and arterial events, and 8 had only arterial thrombosis. Sites of the first thrombotic event of the 38 patients with LAC were deep vein thrombosis (DVT) in 19 (50%) patients, pulmonary embolism (PE) in 4 (11%), DVT combined with PE in 5 (13%), ischemic stroke in 6 (16%), myocardial infarction in 3 (8%), and ischemic microcerebrovascular event concomitant with livedo reticularis (Sneddon's syndrome) in one (2%). Twelve of the 28 venous thromboses were apparently spontaneous, while 16 occurred while taking oral contraception (n = 12), after delivery (n = 2), or

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Table 1. Demographic and descriptive data of LAC-positive patients with and without thrombosis and healthy controls. Values are given as median and interquartile range (IQR).

	LAC with Thrombosis	LAC without Thrombosis	Controls
No. of patients	38	27	33
Sex, F/M	34/4	19/8	25/8
Age at study entry, yrs	40.8 (30.7–54.7)	57.5 (38.7–68.5)	44.9 (38.6–56.4)
Time from diagnosis to study entry, yrs	2.2 (0.7–7.4)	1.9 (1.2–3.7)	
Body mass index, kg/m^2	25.7 (22.5–28.8)	24.9 (23.1–27.7)	22.5 (21.1–24.5)
Current smokers (%)	11 (29)	11 (41)	9 (27)
Blood group O (%)	12/35* (34)	9/24* (36)	10/30* (33)
aCL IgG (GPL/ml)	66.3 (9.4–124.5)	9.8 (5.1–33.0)	4.4 (2.3–7.8)
Increased levels (%)	23 (61)	11 (41)	0
aCL IgM (MPL/ml)	9.5 (6.0–22.4)	14.4 (7.9–37.6)	3.9 (3.0–6.6)
Increased levels (%)	17 (45)	16 (59)	2 (6)

* Number of patients with available data on blood group.

postsurgically (n = 2). Eighteen patients (47%) had at least one recurrent thrombotic event. Twenty-nine of the 38 patients with thrombosis were taking continuous oral anticoagulation at enrolment.

Patients with and without thrombosis were equally exposed to situations associated with an increased risk of thrombosis during their lifetime by surgery [35/38 (92%), 25/27 (93%)] and episodes of trauma [19/38 (50%), 15/27 (56%)]. The occurrence of pregnancy and exposure to oral contraception was documented in 28 (82%) and 24 (71%) of the 34 women with thrombosis as well as in 12 (63%) and 11 (58%) of the 19 women without thrombosis.

Hereditary risk factors for thrombosis were noted in 15 LAC-positive patients with thrombosis, 9 patients without thrombosis, and in 8 healthy controls. Three LAC-positive patients with thrombosis and 4 healthy controls were heterozygous for the factor V:R506Q mutation and one LAC-positive patient without thrombosis was homozygous. Two patients with thrombosis and 2 controls were heterozygous carriers of the factorII:G20210A gene mutation: none was homozygous. Only one patient in the thrombosis group had antithrombin deficiency. No patient had protein C or protein S deficiency. Hyperhomocysteinemia was found in 11 LAC-positive patients with thrombosis, in 8 LAC patients without thrombosis, and in 4 controls.

Significantly higher levels of markers of inflammation were observed in patients with LAC with (hs-CRP median 0.3 mg/dl, IQR 0.1–0.63; fibrinogen mean 395 ± 90 mg/dl; factor VIII mean 181 ± 50%) and in those without thromboembolism (hs-CRP median 0.21 mg/dl, IQR 0.09–0.67; fibrinogen mean 377 ± 91 mg/dl; factor VIII mean 179 ± 78%) in comparison to the levels in controls (hs-CRP median 0.07 mg/dl, IQR 0.03–0.12; fibrinogen mean 308 ± 49 mg/dl; factor VIII mean 137 ± 39%). The results are illustrated in Figure 1. After adjustment for age, BMI, smoking status, and blood group (covariate only for factor VIII) differences in CRP and factor VIII levels remained significant comparing LAC-positive patients to controls, while fibrinogen levels remained significantly different only between LAC-positive patients with thrombosis and controls (Table 2).

Using linear regression, the presence of LAC was significantly correlated with markers of inflammation (hs-CRP $p < 0.001$, fibrinogen $p < 0.001$, factor VIII $p < 0.001$). aCL IgM antibodies showed a significant association only with hs-CRP ($p = 0.004$), but not with fibrinogen ($p = 0.154$) or with factor VIII ($p = 0.321$); aCL IgG antibodies did not show a significant association with any marker of inflammation.

No differences in markers of inflammation were found between LAC-positive patients with and those without thrombosis (Figure 1, Table 2).

Markers of inflammation in the 12 patients with an arterial thrombotic event in their history (hs-CRP median 0.52 mg/dl, IQR 0.07–0.87; fibrinogen mean 403 ± 89 mg/dl; factor VIII mean 177 ± 41%) did not differ statistically significantly from the 26 patients with only venous thromboembolic events (hs-CRP median 0.26 mg/dl, IQR 0.13–0.55, $p = 0.967$; fibrinogen mean 392 ± 92 mg/dl, $p = 0.936$; factor VIII mean 182 ± 55%, $p = 0.976$) and from the 27 LAC-positive patients without thrombosis (hs-CRP median 0.21 mg/dl, IQR 0.09–0.67, $p = 0.842$; fibrinogen mean 377.3 ± 91.1 mg/dl, $p = 0.707$; factor VIII mean 179.3 ± 78%, $p = 0.995$).

If patients with a concomitant autoimmune disease, mainly systemic or incomplete SLE, were excluded from analysis (n = 24), we still observed statistically significantly higher levels of markers of inflammation in LAC-positive patients with thrombosis (hs-CRP median 0.25 mg/dl, IQR 0.09–0.59, $p < 0.001$ vs controls; fibrinogen mean 382.9 ± 86.6 mg/dl, $p = 0.001$; factor VIII mean 173.0 ± 49.2%, $p = 0.022$) and those without thrombosis (hs-CRP median 0.19 mg/dl, IQR 0.09–0.58, $p = 0.011$; fibrinogen mean 360.5 ± 85.9 mg/dl, $p = 0.045$) except for factor VIII (mean 156.6 ± 60.4%, $p = 0.397$). There was no significant difference

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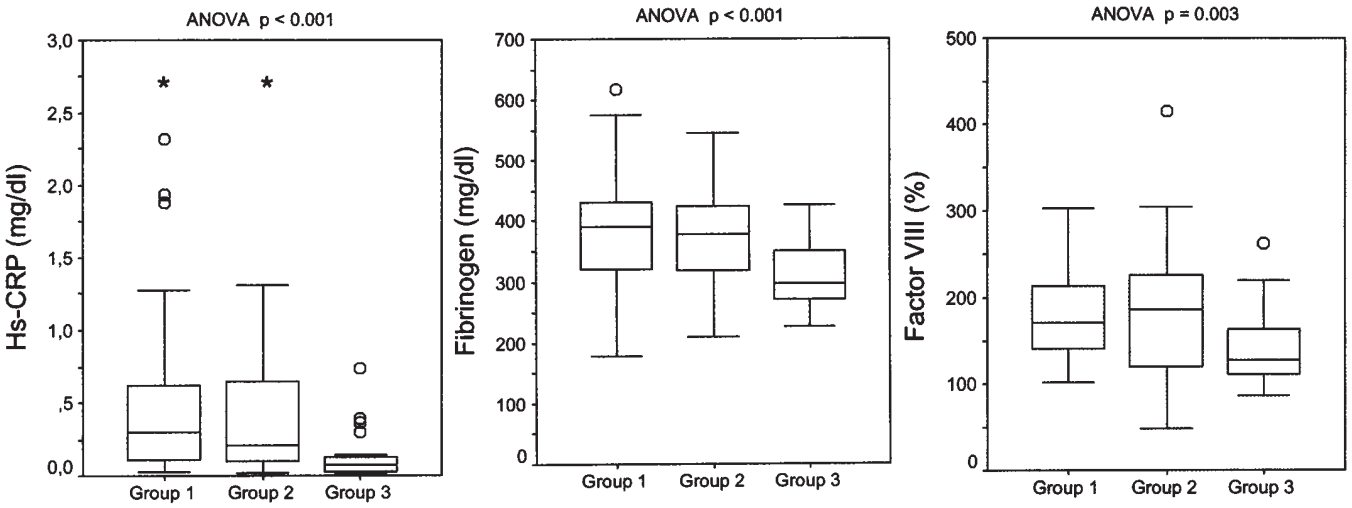

Figure 1. Box blots comparing levels of 3 inflammatory markers in LAC groups and healthy controls. Group 1: LAC-positive patients with a history of thrombosis; Group 2: LAC-positive patients with no history of thrombosis; Group 3: healthy controls. ○: hs-CRP levels between the 1.5- and 3-fold interquartile range (IQR); *hs-CRP levels outside the 3.0 IQR (all > 3.0 mg/dl in our series). Significance (p) values derived using analysis of variance (ANOVA) are shown.

between LAC-positive patients with and those without thrombosis (p = 0.628 for hs-CRP, p = 0.587 for fibrinogen, p = 0.529 for factor VIII).

Applying a multivariable logistic regression analysis, markers of inflammation were not associated with thromboembolism (hs-CRP: p = 0.561; fibrinogen: p = 0.347, factor VIII: p = 0.525). Interestingly, patients with elevated aCL IgG carried a 3.8-fold (95% CI 1.2–12.2) increased risk of thrombosis in contrast to those with normal levels. aCL IgM antibodies were not associated with thrombosis in patients with LAC. Patients with an established risk factor for thrombosis did not have an increased risk for thrombosis in our study population.

Correlation analyses were performed among LAC-positive patients. A strong positive correlation was present between hs-CRP and fibrinogen (r = 0.65, p < 0.001), whereas factor VIII did not correlate with hs-CRP (r = 0.243, p = 0.18). BMI was highly associated with hs-CRP (r = 0.431, p < 0.001) and fibrinogen (r = 0.359, p < 0.001), but was not correlated with factor VIII (r = 0.024, p = 0.817). There was only a weakly positive relationship between age and hs-CRP (r = 0.224, p = 0.029), fibrinogen (r = 0.237, p = 0.019), and factor VIII (r = 0.226, p = 0.025).

DISCUSSION

This study shows that the LAC is associated with elevated markers of systemic inflammation irrespective of the presence of SLE. Markers of inflammation did not correlate with a history of thrombosis in patients with the LAC.

We found elevated hs-CRP levels in our cohort of LAC patients compared to the controls. However, hs-CRP levels were not significantly different between LAC-positive patients with and those without thrombosis. CRP is an established risk factor for arterial thrombosis[25-27], whereas its role in venous thrombosis is controversial. In a case control study CRP levels were observed to be higher in patients with a history of venous thromboembolic events compared to controls[28]. On the other hand, elevated CRP levels were not associated with venous thrombosis in 2 prospective studies[29,30]. Linear regression analysis revealed a strong association between CRP and LAC as well as aCL IgM. In various autoimmune diseases and viral as well as bacterial infections, elevated aCL and an inflammatory state are concomitantly found[31,32]. However, aCL found in infectious disease are distinct from those detected in autoimmune disease. The influence of aCL on the development of thrombosis in infectious diseases is controversial, but most probably is much

Table 2. Comparison of markers of inflammation (p values) between LAC patients with thrombosis (Group 1), LAC patients without thrombosis (Group 2), and healthy controls (Group 3), unadjusted and adjusted for age, BMI, smoking status, and blood group (only for factor VIII).

	Group 1 vs Group 2		Group 1 vs Group 3		Group 2 vs Group 3	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Hs-CRP	0.829	0.423	< 0.001	0.002	< 0.001	0.044
Fibrinogen	0.649	0.287	< 0.001	0.026	0.003	0.420
Factor VIII	0.996	0.706	0.005	0.003	0.015	0.046

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less strong[33,34]. Interestingly, only aCL IgM and not IgG showed a significant association with hs-CRP. It is possible that the increase of aCL IgM and CRP might be stimulated by a similar mechanism, whereas different triggers are responsible for the production of aCL IgG.

Our data showed no association between fibrinogen levels and thrombosis in LAC-positive patients. This is in contrast to previous findings from our group and another study indicating that the occurrence of thrombosis might be associated with elevated fibrinogen levels in LAC-positive patients[35,36]. However, those studies included a relatively small number of patients. In this study, more patients were investigated and only patients with long-lasting persistent LAC were included. The role of fibrinogen as a risk factor for venous thrombosis in general is not clear. Koster, *et al* showed that the thromboembolic risk is related to plasma fibrinogen levels[37], while other investigators reported contradictory data[30,38]. As a positive correlation between fibrinogen and CRP was found, we believe that elevated fibrinogen levels in our LAC-positive patients also reflect an increased state of inflammation in those with LAC.

Factor VIII has gained importance as a definite risk factor for venous thrombosis, as several studies showed a relationship between the primary and recurrent thrombosis risk and the level of factor VIII[30,39,40]. In addition an elevated factor VIII level also increases the risk of thrombosis at the arterial site[41,42]. In our study no association between the occurrence of thrombosis in the LAC group and factor VIII level was evident. It might be hypothesized that an increased factor VIII level by itself does not increase the risk for thrombosis, but rather reflects a distinct prothrombotic stimulus, which is probably not present in LAC patients. Interestingly, we found no significant correlation between factor VIII and CRP levels, in accord with findings of O'Donnell, *et al* in patients without LAC[43]. This strengthens the hypothesis that factor VIII levels are influenced by factors other than inflammation, such as LAC itself, age, BMI, smoking status, and blood group.

Using multivariable logistic regression analysis, markers of inflammation did not indicate the risk of thrombosis in patients with LAC. There was an association between aCL IgG and thromboembolism, which we did not find with the IgM isotype. Established risk factors for thrombosis were not found to predispose to thrombosis in our patients with LAC, which might be due to the small number of patients with additional risk factors, or to the strength of LAC itself as a thrombotic risk factor.

Arterial thrombosis with LAC is more likely due to thrombogenesis rather than atherogenesis, although the atherosclerotic process may be enhanced by antiphospholipid antibodies[44]. Markers of inflammation, namely CRP and fibrinogen, proved to constitute an independent risk factor for coronary heart disease and stroke, and may have the ability to predict the cardiovascular risk[45,46]. When we compared LAC-positive patients with arterial thrombosis to LAC-positive patients with only venous thrombosis, and to those without thrombosis, we found no association between inflammation and arterial thrombosis. However, definite conclusions on the role of inflammation in arterial thrombosis in LAC-positive patients cannot be drawn due to the small number of patients with arterial events.

In accord with previous findings, CRP and fibrinogen were positively correlated with BMI[47-50]. There was only a weak positive correlation between the investigated markers of inflammation and age. Thus, differences in age between groups might have only marginally influenced the results. Indeed, adjustment for potential confounding factors did not markedly change the results.

It is noteworthy that our patients with a history of thrombosis were younger than those without. This observation is in contrast to the fact that venous thrombosis is more likely to occur at an advanced age. It could be hypothesized that different entities of the LAC exist and that the clinically relevant form appears predominantly in women at young age, whereas clinically irrelevant forms are found at any age. A classic example for the latter is the transient LAC seen in children who rarely develop thrombosis[51].

A limitation of our study is its retrospective design, since we cannot exclude the possibility that LAC-positive patients with no history of thrombosis may develop a thrombotic event later during the course of their disease. On the other hand our data are strengthened by the fact that only patients with persistent and long-lasting LAC were included.

A marker for disease activity would be useful in clinical practice to estimate the severity and clinical course of disease. Markers of inflammation are used as predictors for disease activity in infectious disease, while their importance in autoimmune disorders is limited. In SLE, systemic markers of inflammation, namely CRP, possess no predictive value for disease activity[52]. According to our data there was a similar situation in LAC-positive patients with respect to development of thrombosis, since elevated levels of markers of inflammation were also present in LAC-positive patients without thrombosis.

Increased markers of inflammation were found in patients with LAC, irrespective of the presence of concomitant SLE. Levels of hs-CRP, fibrinogen, and factor VIII activity were not associated with the occurrence of thromboembolism in patients with LAC.

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