Imbalance of Thromboxane/Prostacyclin Biosynthesis in Patients With Lupus Anticoagulant

By Franck Lellouche, Marta Martinuzzo, Patricia Said, Jacques Maclouf, and Luis O. Carreras

The mechanism involved in the association between antiphospholipid antibodies and thrombosis or fetal loss remains unclear. We assessed the biosynthesis of thromboxane A₂ and prostacyclin in 31 samples from 25 patients with lupus anticoagulant and in 32 controls. The urinary excretion of the major thromboxane metabolite of platelet origin (11-dehydro-thromboxane B₂) was very significantly increased (P < .0003) in the patients. In contrast, the urinary metabolite reflecting the vascular production of prostacyclin (2,3-dinor-6-keto-prostaglandin F₁α) was much less increased (P < .02). We found no correlation between the levels of antcardiolipin antibodies and the urinary excretion of 11-dehydro-thromboxane B₂. Six patients with elevated urinary 11-dehydro-thromboxane B₂ were treated with low-dose aspirin (20 mg/d during 7 days). In these patients, there was a close relationship between the extent of inhibition of the thromboxane urinary metabolite (72%) and serum thromboxane B₂ (79%). In contrast, the urinary excretion of 2,3-dinor-6-keto-prostaglandin F₁α was nearly unchanged (13% reduction). In addition, the F(α') fragments isolated from six patients presenting increased urinary 11-dehydro-thromboxane B₂ enhanced the generation of thromboxane B₂ (P = .04) and the release of [³C] serotonin (P = .009) by normal washed platelets, as compared with F(α') from controls. In summary, our study shows that in patients with lupus anticoagulant, platelet activation may occur without a compensatory increase in the vascular biosynthesis of prostacyclin. This observation may be crucial to cause or reflect an increased risk for thrombosis. In addition, our results may suggest a rationale for antiplatelet agents for the prophylaxis of thrombosis in many patients with the antiphospholipid syndrome.

Thromboxane (TX) A₂ and prostacyclin (PGI₁) are the major prostanooids formed by platelets and vessel wall, respectively. Both are chemically very unstable compounds that undergo rapid hydrolysis to TXB₂ and 6-keto-prostaglandin-F₁α (6-keto-PGF₁α). Because of their potent and contrasting effects on platelet activation and vascular tone, an abnormal TXA₂/PGI₁ ratio may predispose affected patients to thrombosis.¹ It has been reported that the lupus anticoagulant (LA) may interfere with the production of PGI₁ by vascular tissues in vitro.² This phenomenon could play a role in the origin of thrombotic events and obstetric complications in patients with LA.³ However, controversial results on the effect of the LA on the generation of eicosanoids by cultured endothelial cells and stimulated platelets have been reported.⁴⁻¹¹ Recent studies have shown that urinary metabolites of TX and PGI₁ constitute unique markers of the activation and/or interaction between platelets and vascular cells. Such approach does reflect the in vivo production of these mediators and has the advantage of circumventing the artifactual production of eicosanoids occurring during blood or tissue sampling.¹²⁻¹³ Thus, such an approach could answer some points raised in the previously mentioned studies in regard to an imbalance of production between TX and PGI₁ in patients with LA.

We have recently developed a technique using thin-layer chromatography/enzyme immunoassay procedure validated by gas chromatography/negative ion chemical ionization mass spectrometry (GC/NICI-MS) for measuring the urinary metabolites of platelet-derived TXA₂ (ie, 2,3-dinor-TXB₂ and 11-dehydro-TXB₂) and of vascular cell-derived PGI₁ (ie, 2,3-dinor-6-keto-PGF₁α).¹⁴ We applied this methodology to evaluate the biosynthesis of eicosanoids in patients with LA.

MATERIALS AND METHODS

Patients. We measured the metabolites of TXA₂ and PGI₁ in the urine of 25 patients (21 females and 4 males) with LA and antiphospholipid (aCL) antibodies detected by the enzyme-linked immunosorbent assay (ELISA) method. The clinical features of our population are shown in Table 1. Informed consent was obtained from all the patients participating in the study. The mean age of our population was 33.7 years (range 14 to 70 years). Thirteen patients had systemic lupus erythematosus (SLE) (eight of them with antiphospholipid (aPL)-related clinical complications), eight patients were diagnosed as primary antiphospholipid syndrome, and the remaining four were asymptomatic. Eight patients had a history of thrombosis (venous thrombosis in five, arterial thrombosis in two, and both types in one). Ten patients had recurrent fetal loss. In two of these cases, both obstetric complications and thrombotic events were observed. All patients had normal renal function and normal platelet count. Thirty-two healthy subjects (15 males and 17 females, nonsmokers, mean age 32 years, range 23 to 42 years) who had not received any drug for at least 15 days before urine collection served as controls.

Detection of the lupus anticoagulant. Blood was obtained by venipuncture from the antecubital vein and collected into plastic tubes containing 0.129 mol/L sodium citrate in a ratio of 9 parts blood to 1 part anticoagulant, and then centrifuged twice at 4°C at 2,500g for 15 minutes. Platelet-poor plasma (PPP) was obtained and assayed immediately. Blood samples for serum tests (detection of aCL antibodies) were collected into glass tubes without anticoagulant at the same time as plasma samples were drawn. The blood was allowed to clot and then was centrifuged at 1,000g for 10
minutes to obtain serum. All coagulation studies were performed in duplicate.

Screening tests performed for the detection of LA were: activated partial thromboplastin time (APTT) using partial thromboplastin extracted from human brain, kaolin clotting time (KCT), and dilute Russell viper venom time (DRVVT).

The prolongation of these phospholipid-dependent coagulation tests was considered to be due to an inhibitor if it was not corrected in a 1:1 (vol/vol) mixture with normal plasma.

To confirm the antiphospholipid nature of the inhibitor, the following tests were used: platelet neutralization procedure (PNP) in both the APTT and DRVVT systems, APTT using high partial thromboplastin concentration, and the tissue thromboplastin inhibition assay (TTI).

A plasma sample was considered to contain an LA when at least one of the screening and one of the confirmatory tests were positive, according to previously defined criteria.16

Detection of anticardiolipin antibodies. aCL antibodies (IgG and IgM isotypes) were measured using a standardized ELISA technique16 with some modifications. Briefly, microtiter plate wells (Flow, Irvine, Scotland) were coated with 50 μL cardiolipin (Sigma, St Louis, MO) dissolved in ethanol (50 μg/mL). The plates were kept overnight at 4°C resulting in a complete evaporation of the ethanol. Nonspecific binding was blocked by incubation of the wells with 120 μL 10% adult bovine serum (Sigma) in a phosphate-buffered saline pH 7.4 (ABS/PBS) for 2 hours at room temperature. The plates were washed three times with 150 μL PBS and 80 μL of patients' sera diluted 1:40 in ABS/PBS was added in triplicate. The first column of each plate was used for control blanks. After a 3-hour incubation period, the plates were washed again with 150 μL PBS per well and incubated for 90 minutes at room temperature with 80 μL goat antihuman IgG or IgM-alkaline phosphatase conjugate (Sigma) diluted 1:1,000 in ABS/PBS. The plates were washed three times with 150 μL PBS/well and 80 μL of p-nitrophenyl phosphate solution (Sigma), 1 mg/mL in diethanolamine buffer pH 9.8 was added to each well, and the plates were incubated for 1 hour at room temperature in the dark. The reaction was stopped by the addition of 80 μL NaOH, 3 mol/L, and the optical absorbance was read at 405 nm using a Titertek Multiskan (Flow Labs, Helsinki, Finland). Sera were also tested for nonspecific binding in wells covered with absolute ethanol in the absence of cardiolipin. Optical absorbance of uncoated plates were subtracted from that of coated plates. As calibration samples, we used reference standard sera, kindly provided by Dr E.N. Harris (University of Louisville, Louisville, KY). The calibration curve for aCL determination was performed according to the recent recommendations of an international workshop17 (and E.N. Harris, personal communication, April 1990). The amount of aCL antibodies was expressed as standard units for either IgG (GPL units) or IgM (MPL units).

Measurement of urinary metabolites of TXA2 and PGF2α. Overnight urines were collected in the morning, fractionated in 50-mL aliquots, and kept frozen at ~7°C until analysis. We used a recently developed enzyme immunoassay (EIA) method for measuring urinary concentrations of 2,3-dinor-6-keto-PGF1α and 11-dehydro-TXB2, using acetylicholinerestase from Electrophorus electricus coupled to 6-keto-PGF1α and 11-dehydro-TXB2.18 Briefly, urinary PGH2 and TXA2, breakdown products and their metabolites were extracted from 3 to 40 mL of urine corresponding to 100 μmol creatinine using Sep-Pak cartridges (Waters, Milford, MA); 1H-TXB2 (Du-Pont, Paris, France; 3.7 to 9.25 TBq/mmol) was added for recovery. Metabolites were further purified by thin-layer chromatography and quantitation was performed by EIA after correction of the values for losses in recovery. This method has been correlated with the results obtained by GC/MS (r = .98).18

Assessment of the effect of low-dose aspirin on eicosanoids generation. Six patients with LA and documented enhanced urinary excretion of 11-dehydro-TXB2 were treated with low-dose aspirin (20 mg/d during 7 days). Measurement of the urinary metabolites of eicosanoids was performed at day 0 and day 7. In parallel, TXB2, from the serum of these patients was assayed on samples prepared the same days by letting the blood clot 45 minutes at 37°C.

IgG purification and obtention of F(ab')2 fragments. Blood was collected by venipuncture without anticoagulant from six patients with increased urinary TXB2 metabolites and three controls and the serum was obtained. One additional control was obtained from a pool of a commercially available human IgG (Immuno AG, Vienna, Austria). The serum was diluted with saline solution and the Ig fraction was precipitated with ammonium sulfate at 50% under continuous stirring for overnight at 4°C. After centrifugation at 10,000g for 10 minutes, the pellet was redissolved in 0.01 mol/L phosphate buffer, pH 7.4 and dialyzed against this buffer at 4°C. The proteins were applied to an ion-exchange chromatography column (DEAE-cellulose; Pharmacia, Uppsala, Sweden). The purity was determined by immunoelectroelphoresis and sodium dodecyl sulfate polyacrylamide gels (SDS-PAGE).19 The purified IgG were then dialyzed in a 0.1 mol/L acetate buffer pH 4.5 for 2 hours at 4°C and pepsin (1%, wt/wt) was incubated for 18 hours at 37°C. The digestion was stopped by dialysis against phosphate buffer at 4°C for 4 hours. The F(ab')2 fragment was purified by gel filtration on a Sephadex G-150 superfine (Pharmacia) column equilibrated with phosphate buffer. The purity was checked by using immunoelectrophoresis and SDS-PAGE.19

Isolation of platelets and stimulation of platelets by F(ab')2. Human venous blood (9 vol) was obtained from adult human volunteers who had not received medication for at least 1 week. Blood was anticoagulated with acid-citrate-dextrose anticoagulant (ACD, National Institute of Health formula A) (1 vol) and centrifuged for 15 minutes at 120g at room temperature. The platelet-rich plasma (PRP) was collected and platelets were

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labeled with \( ^{14} \text{C}- \) serotonin (Amersham Radiochemical Centre, Amersham, UK), 0.5 \( \mu \text{Ci} / 10 \text{mL PRP} \) during a 30-minute incubation at room temperature. The PRP was further acidified to pH 6.5 by addition of \( 1/60 \text{ vol ACD-A} \) and centrifuged for 15 minutes at 400g. The platelets were washed using a citrate buffer pH 6.5 containing 4 g/L bovine serum albumin and \( 10^{-7} \text{ mol/L prostaglandin E}_2 \), according to the method described by Patscheke.

The platelet pellet was finally resuspended in a calcium and magnesium free Hanks buffer pH 7.4 and the cells were adjusted at a concentration of \( 200 \times 10^9 / \text{L} \).

Washed platelets (300 \( \mu \text{L} \)) were incubated during 15 minutes at room temperature with \( 50 \mu \text{L} \text{ F(ab')}_2 \) fractions from patients and controls at a final concentration of 0.5 to 1 ng/mL. Then 50 \( \mu \text{L} \) of a calcium/magnesium solution was added at a final concentration of 2 and 1 mmol/L, respectively. The cuvette was incubated at \( 37^\circ \text{C} \) into a Payton aggreometer (Payton Associates, Buffalo, NY). After 3 minutes, the platelets were transferred to an Eppendorf tube containing 100 \( \mu \text{L} \) of ice-cold 0.1 mol/L EDTA and immediately centrifuged for 1 minute at 11,000g in an Eppendorf centrifuge. An aliquot of the supernatant was used for the determination of the \( ^{14} \text{C}- \) serotonin release and the remainder was kept frozen for TXB\(_2\) measurement by EIA. Release was expressed as percent of total incorporated \( ^{14} \text{C}- \) serotonin.

Statistical analysis. Comparison of the urinary excretion of eicosanoids between patients and controls was performed by unpaired two-tailed \( t \)-test. Comparison of the urinary metabolites and of the TXB\(_2\) in serum before and after 7 days of low-dose aspirin administration was performed by a two-tailed \( t \)-test for paired data (\( t \)-ease; Institute for Scientific Information Software, Philadelphia, PA). The Pearson correlation coefficient was used to compare the titers of aCL antibodies and APTT prolongation with the urinary excretion of eicosanoid metabolites.

RESULTS

All the patients' sera had aCL antibodies detected by ELISA at high (> 100 GPL units or > 60 MPL units) or moderate level (20 to 100 GPL units or 20 to 60 MPL units) in addition to the LA.

Determination of the urinary excretion of TXA\(_2\), and PG\(_I\)\(_2\) metabolites showed a significantly increased excretion of 11-dehydro-TXB\(_2\) in 25 patients with LA as compared with 32 healthy individuals (141 ± 25 \( v \) 33.7 ± 2.9 ng/mmol creatinine, respectively, \( P < .0003 \)). We found no significant difference between patients with or without SLE (128 ± 21 \( v \) 107 ± 19 ng/mmol creatinine, respectively, \( P = .48 \)). In contrast, we found minor modifications of 2,3-dinor-6-keto-PGF\(_{1\alpha}\) (22.3 ± 2.4 \( v \) 15.1 ± 1.3 ng/mmol creatinine, \( P < .02 \)) (Fig 1). In three patients with LA and aCL antibodies, we measured the urinary eicosanoid metabolites on three occasions over a 1-year period. Although there were some intra-individual fluctuations throughout time, the values of 11-dehydro-TXB\(_2\) were consistently elevated whereas 2,3-dinor-6-keto-PGF\(_{1\alpha}\) remained within the range of control values (Table 2).

There was no correlation between the level of aCL antibodies or APTT prolongation and the urinary excretion of 11-dehydro-TXB\(_2\), or 2,3-dinor-6-keto-PGF\(_{1\alpha}\) (Table 3).

To assess the cellular origin of the elevated urinary TXA\(_2\) metabolites, aspirin was given at a cumulative low dose to six patients previously recognized for their elevated values of 11-dehydro-TXB\(_2\). After 7 days of ingestion, there was a significant reduction of urinary 11-dehydro-TXB\(_2\) (72%) related to the inhibition of TXB\(_2\) generated in serum (79%) when comparing values at day 0 and day 7. In contrast, the production of 2,3-dinor-6-keto-PGF\(_{1\alpha}\) was nearly unchanged (13% reduction).

Figure 2 shows that the incubation of normal washed platelets with F(ab')\(_2\) fragments from some patients with LA and elevated levels of urinary 11-dehydro-TXB\(_2\) generated enhanced production of TXB\(_2\), as compared with the F(ab')\(_2\) from controls (6.1 ± 0.6 ng/mL \( v \) 4.3 ± 0.49 ng/mL, \( P = .04 \)). A more enhanced effect was observed on the release of \( ^{14} \text{C}- \) serotonin (3.6% ± 0.7% \( v \) 0.7% ± 0.3%, \( P = .009 \)). Experiments have been performed on two to three different sets of normal platelets for each F(ab')\(_2\) (controls and patients).

DISCUSSION

aCL antibodies as well as the LA are associated with thromboembolic phenomena, repeated fetal loss, and thrombus...
bocytopenia.2,21,22 The term “anticardiolipin antibody syndrome” and more recently “antiphospholipid syndrome” have been proposed to describe this particular group of patients.23

Despite considerable interest in this syndrome over the last few years the mechanisms implicated in the association between antiphospholipid (aPL) antibodies and thrombosis remains unclear.4 Several investigators have reported that the LA may interfere with the production of PGI2 by vascular tissues.24 It has been postulated that the inhibition of PGI2 production could play a role in the origin of thrombotic events and obstetric complications in these patients.2,3

However, some controversial results on the effect of the LA on the generation of PGI2 by endothelial cells in culture have also been reported.8-11 These results of in vitro experiments could partially be related to methodologic aspects.8 For example, they could be influenced by the source of endothelial cells, the presence or absence of the Ig containing the LA in the incubation medium during the stimulation experiments, or agents used to stimulate PGI2 synthesis.

On the other hand, it has been observed that the sera of some patients with SLE and aPL antibodies may enhance the generation of TXB2 by PRP stimulated with collagen or arachidonic acid.11 In contrast, it has been reported that LA may inhibit the formation of TXB2 by thrombin-stimulated platelets.7

Our study proves that an abnormal synthesis of eicosanoids occurs in vivo in some patients with LA, leading to an imbalance in the TXA2/PGI2 ratio. We found a very significant increase in the urinary excretion of TXA2 metabolites of platelet origin. In our patients with SLE, this abnormality may not be attributed to the underlying disease. In a previous study, Patrono et al25 have shown that only urinary TXB2 and 6-keto-PGF1α were affected in patients with SLE but without LA, whereas the platelet-derived urinary metabolite 2,3-dinor-TXB2 was unchanged. In addition in our selected population with aPL antibodies we found no difference in the excretion of TXA2 metabolites of platelet origin between patients with SLE and those without any underlying disease. On the other hand, the marked increase in urinary excretion of these metabolites in our patients as compared with the control group may not be related to differences in sex,25,26 age distribution,27 or platelet count28 (none of the patients was thrombocytopenic at the time of the study). In a subgroup of 15 patients with LA we have also found a significantly enhanced urinary excretion of 2,3-dinor-TXB2 (not shown), similar to that of 11-dehydro-TXB2, shown here. We subsequently monitored exclusively 11-dehydro-TXB2. Thus, our results suggest that the enhanced excretion of TX metabolites reflects a change in the in vivo production of TX rather than a shift in its metabolic fate. Furthermore, in three patients with elevated urinary 11-dehydro-TXB2, the excretion of this metabolite was consistently abnormal in three consecutive measurements performed over a 1-year period. Two of these patients had primary antiphospholipid syndrome. This finding would suggest that in vivo platelet activation is a permanent, rather than a transient, phenomenon in these patients. In additional experiments, to strengthen the assumption that the observed increase of TX was derived from platelets, we treated six patients with low-dose aspirin (20 mg/d during 7 days). Measurements of the urinary metabolites showed a selective reduction of TX metabolites parallel to the inhibition of TX generated in serum and minor modification of the 2,3-dinor-6-keto-PGF1α. These results are in agreement with previous reports showing a
selective inhibition of platelet-derived products with sparing of the vascular enzyme.\textsuperscript{20,30}

Arfors et al\textsuperscript{11} have recently reported an increased excretion of 2,3-dinor-TXB\textsubscript{2} in patients with aPL antibodies which, they hypothesized, could be derived from platelets. Our study differs on the fact that all patients were selected because of the presence of LA activity.

We have also shown that F(ab\textsuperscript{'})\textsubscript{2}, fragments isolated from the sera of some patients with aPL antibodies and presenting increased levels of urinary 11-dehydro-TXB\textsubscript{2} induced a small but significant activation of normal washed platelets as reflected by the generation of TXB\textsubscript{2} and the release of \textsuperscript{14}C-serotonin. In addition, the potential platelet-activating effect of the antibodies could be weakened by an unavoidable damage of the binding sites during the F(ab\textsuperscript{'})\textsubscript{2} preparation and purification. It has been reported earlier\textsuperscript{22} that aCL antibodies may bind platelets, but perturbation of the membrane seems to be a prerequisite. Such perturbation could be consecutive to the washing procedure and we could indeed suppress the activation by pretreating the platelets by prostaglandin E\textsubscript{1}. In view of the association between aCL antibodies and increased urinary TX metabolite excretion, our results suggest that these antibodies could contribute to the activation of platelets in vivo, in addition to other mechanisms. However, the lack of correlation between the level of aCL antibodies and urinary excretion of TX\textsubscript{A2} metabolites is not surprising. In principle, phospholipid binding antibodies are heterogeneous and their activating effect on platelets may not be directly related to titer or isotype (as detected by ELISA method) or their inhibitory activity on blood coagulation. This poor correlation could also be related to some extent to the distinct half-life of Igs, platelets, and eicosanoid metabolites.

In general, a concomitant increase in the biosynthesis of TX\textsubscript{A2} and PGI\textsubscript{2} has been observed in a number of conditions associated with increased platelet turnover.\textsuperscript{33,35} This suggests that the enhanced synthesis of PGI\textsubscript{2} may represent (or reflect) a compensatory response of vascular endothelium to platelet activation.\textsuperscript{34} Moreover, an enhanced in vivo biosynthesis of PGI\textsubscript{2} in patients with severe atherosclerosis\textsuperscript{36} occurs despite a reduced capacity of atherosclerotic blood vessels to generate PGI\textsubscript{2} in vitro.\textsuperscript{36} In our study, the urinary metabolites considered to reflect the vascular production of PGI\textsubscript{2} were only slightly increased as compared with normal controls. This may reflect an abnormal compensatory response of the vessel wall to platelet activation.

In summary, our study shows that LA would create a rather unique abnormality with concomitant platelet activation and TX\textsubscript{A2} generation associated to a failure of the vessel wall to produce increased amounts of the natural platelet inhibitory compound PGI\textsubscript{2}. This phenomenon may be crucial to generate an increased risk for thrombosis in patients with LA.

Overall, our results may suggest a rationale for antiplatelet agents (in particular cyclooxygenase inhibitors) for the prophylaxis of thrombosis in these patients.

REFERENCES


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Imbalance of thromboxane/prostacyclin biosynthesis in patients with lupus anticoagulant

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