Antiphospholipid Antibodies Directed Against a Combination of Phospholipids With Prothrombin, Protein C, or Protein S: An Explanation for Their Pathogenic Mechanism?

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Despite many studies on the pathophysiology of antiphospholipid antibodies (aPL), the mechanism by which aPL causes thrombosis has not been established. We have tried to elucidate the paradox between the prolongation of the clotting time of phospholipid-dependent coagulation tests in vitro and the occurrence of thrombosis in vivo. The effect on endothelial cell-mediated prothrombinase activity of 30 IgG fractions, of which 22 prolong the aPTT of normal plasma, was investigated. Only 4 of 22 fractions (18%) inhibited prothrombinase activity when tested on this more physiologic phospholipid surface, indicating that in most patients with aPL the prolongation of clotting tests is predominantly an in vitro phenomenon. It was recently reported that in detection methods for aPL, two plasma proteins, β2-glycoprotein I and prothrombin, enhance the binding of aPL to phospholipids. We have studied the specificity of the 4 IgG fractions that inhibit the prothrombinase activity and found that they were directed against a combination of phospholipids and prothrombin. However, the involvement of prothrombin in binding of aPL leading to impaired the conversion of fibrinogen to fibrin, the endproduct of coagulation. The anticoagulant function is the binding to the endothelial cell receptor thrombomodulin. Bound to thrombomodulin, thrombin has lost its procoagulant functions and can activate the important anticoagulant protein, protein C. We studied the effect of 30 IgG fractions, of which 22 prolong the aPTT of normal plasma on the prothrombinase activity on endothelial cells (EC), a more physiologic surface than the phospholipids commonly used in LAC tests. It was found that only a minority of the IgG fractions could inhibit the EC-mediated prothrombinase activity. This indicates that LAC can be regarded as an in vitro phenomenon.

Furthermore, we studied the specificity of the IgG fractions that inhibited prothrombinase activity and found that they were not directed to phospholipids, but to a complex of phospholipids and prothrombin. This is in agreement with recently published evidence that for LAC tests and anticardiolipin ELISA, the phospholipid-binding proteins thrombomodulin and β2-glycoprotein I (β2-GPI) are necessary for optimal detection of aPL. Whether the inhibition of prothrombinase activity by antibodies to a combination of phospholipids and prothrombin will result in a loss of predominantly anticoagulant or procoagulant functions of thrombin remains to be investigated.

The effect of aPL has been investigated on several regulatory mechanisms in hemostasis, such as prostacyclin synthesis, fibrinolysis, and protein C activation. This has not led to a general mechanism that explains the frequent occurrence of thrombotic complications in patients with aPL. One explanation might be that aPL is a heterogenous population of antibodies that, depending on the specificity, can interfere with different procoagulant and anticoagulant reactions. This idea is supported by the observation that two different phospholipid-binding proteins (β2-GPI and pro-
thrombin) can enhance binding of aPL. This could indicate that also other plasma proteins might support the binding of aPL. Therefore, we hypothesized that aPL contain subpopulations of antibodies directed against epitopes formed by both phospholipids and phospholipid-binding proteins with anticoagulant functions. Protein C and protein S seem good candidates because they have important physiologic anticoagulant functions that may be impaired by binding of aPL that can result in thrombosis.

Protein C is a vitamin K-dependent plasma protein that can be activated by the thrombin-thrombomodulin complex. After activation, protein C inactivates, together with its cofactor protein S, the clotting factors Va and VIIIa. The importance of protein C and protein S is shown by the association of a (partial) deficiency of protein C or S and thromboembolism.

It has already been described that aPL isolated from some patients can inhibit protein C activity. To investigate if aPL are directed against a combination of phospholipids and protein C or protein S, we studied IgG fractions from the same 30 aPL- and/or thrombosis-positive patients. It was found that 7 IgG fractions could interfere with the anticoagulant activity of protein C and S. Using adsorption studies with phospholipid vesicles, it was shown that the inhibiting IgGs were directed against a combination of phospholipids and activated protein C with or without protein S.

These results support the hypothesis that the heterogeneous population of aPL contains subpopulations of antibodies directed against a combination of phospholipids and different plasma proteins. The identity of the plasma proteins involved in the binding might determine which pathogenic mechanism causes thrombosis.

**MATERIALS AND METHODS**

**Patients and Blood Samples**

Thirty patients (28 females and 2 males) seen at the University Hospital Utrecht (Utrecht, The Netherlands) were selected for this study based on the presence of aPL and thrombosis (Table 1). Twenty patients were diagnosed with systemic lupus erythematosus (SLE), according to the American Rheumatism Association (ARA) criteria; 9 had manifestations compatible with SLE but meeting less than four ARA criteria (lupus-like disease [LLD]); and 1 had no abnormalities suggesting systemic disease and was classified as having primary antiphospholipid syndrome (PAPS). Their median age was 34 years (range, 19 to 66 years). The median duration of disease was 9 years (range, 0.5 to 35 years). Both LAC and anticardiolipin antibodies (aCL) were present in 20 patients, LAC but no aCL in 2 patients, and aCL but no LAC in 4 patients (Table 1). Twenty-three patients had a history of thrombotic complications. Thrombosis was located in venous vessels in 12 patients, in arterial vessels in 10 patients, and in both vessel types in 1 patient. Of the 21 women who had been pregnant, 12 had a history of fetal loss. A plasma pool of 40 healthy donors served as a control.

Blood samples for LAC determination were collected by venipuncture in plastic tubes containing 3.8% (wt/vol) trisodium citrate (0.129 mol/L; 9:1, vol/vol) and centrifuged twice at 4°C for 2,000g for 15 minutes. Blood samples for the preparation of serum were collected by venipuncture into glass трубка. The blood was allowed to clot at room temperature for 1 hour and centrifuged twice at 1,000g for 10 minutes. Platelet-poor plasma and serum were stored at −80°C until use.

| Table 1. Characteristics of Patients |
|---|---|---|---|---|---|---|
| Patient No. | Thr | LAC | aCL | PA | Va Inact. |
| 1 | + | + | + | ↓ | ↓ |
| 2 | + | + | + | ↓ | ↓ |
| 3 | + | + | N | N | ↓ |
| 4 | + | + | N | N | N |
| 5 | + | + | + | N | N |
| 6 | + | − | + | N | N |
| 7 | + | + | + | N | N |
| 8 | + | + | + | N | N |
| 9 | + | + | N | ↓ | ↓ |
| 10 | + | + | + | N | N |
| 11 | + | + | + | N | N |
| 12 | + | + | N | N | N |
| 13 | + | + | N | N | N |
| 14 | + | + | + | N | N |
| 15 | + | + | + | ↓ | ↓ |
| 16 | + | + | + | N | N |
| 17 | + | − | + | N | N |
| 18 | + | + | N | N | N |
| 19 | + | + | + | N | N |
| 20 | + | + | N | N | N |
| 21 | − | + | N | N | N |
| 22 | − | + | N | N | N |
| 23 | − | + | N | N | N |
| 24 | − | + | N | N | N |
| 25 | + | − | N | N | N |
| 26 | − | + | N | N | N |
| 27 | − | − | N | N | N |
| 28 | + | − | N | N | N |
| 29 | − | − | N | N | N |
| 30 | − | + | N | N | N |

Characteristics of 30 patients with (+) or without (−) a history of thrombotic complications (Thr), LAC, or aCL. The effect of IgG on EC-mediated prothrombinase activity (PA) and on APC-mediated factor Va inactivation (Va Inact.) in the absence (−) or presence (+) of protein S is summarized.

**Detection of aPL**

**LAC**. Three LAC assays were performed as described before:
(1) Kaolin clotting time; (2) partial thromboplastin time (PTT) of 1:1 mixture of patient and pooled normal plasma with human brain thromboplastin; and (3) phospholipid dilution test. LAC-positive patients were positive in at least two of these three assays.

**aCL**. IgG- and IgM-aCL were measured with an ELISA as described before.

**Purification of Proteins**

IgG was purified from plasma with protein G- sepharose 4FF (Pharmacia, Uppsala, Sweden) according to the manufacturer’s instructions as described before. On sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), only the IgG was detected with silver staining. Furthermore, with Western blotting, no contamination with β2-GPI was found. IgG purified from LAC- or aCL-positive patients was still positive in these tests.

Prothrombin, protein C, protein S, factor V, factor X, and β2-GPI were purified as described before. Factor V and protein C were activated as described previously. Factor X was activated essentially according to Bock et al.

All proteins were of human origin.

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EC Culture

Human umbilical vein EC (HUVEC) were isolated according to the method of Jaffe et al.27 with some modifications. The cells were cultured in RPMI-1640 (GIBCO Europe Ltd, Paisley, UK) containing 10% fetal calf serum (FCS), 150 μg/mL endothelial cell growth supplement (ECGS; which was prepared according to Maciag et al.), 5 U/mL heparin, 100 U/mL penicillin, 100 μg/mL streptomycin, and 8 μg/mL amphotericin B. Subcultured cells from the third passage were used as confluent monolayers.

EC-Mediated Prothrombinase Activity

Confluent monolayers of EC in 96-well plates were washed three times with an HEPES buffer (25 mmol/L HEPES, 135 mmol/L NaCl, 5 mmol/L KCl, 0.3% bovine serum albumin [BSA], 5 mmol/L glucose, pH 7.4) and preincubated for 60 minutes with patient or normal pooled IgG (7 mg/mL, 37°C) in HEPES buffer containing 5 mmol/L CaCl2. Then prothrombin (1 μmol/L) and factor Va (23.7 pmol/L) were added and the reaction was started by the addition of factor Xa (500 pmol/L). Samples were taken at different time intervals from the supernatant (25 μL) and added to EDTA (75 μL, 25 mmol/L, pH 7.4) to inhibit the prothrombinase activity. The amount of thrombin generated was determined with a chromogenic substrate of the clotting factors, a time-dependent linear increase of thrombin generation was found up to 60 minutes. The effect of patient IgG on the thrombin generation was tested in at least three independent experiments with different EC batches. When the assay was performed with control wells without EC, no thrombin generation was detected.

Factor Va Inactivation by Activated Protein C (APC)

The effect of purified IgG on the factor Va inactivation by APC in the presence or absence of protein S was determined according to the method of Malau et al.,25 with some modifications. In short, cephalin (Boehringer Mannheim GmbH, Mannheim, Germany) was preincubated with control or patient IgG (7 mg/mL) in Tris-buffered saline (TBS; 50 mmol/L Tris, 150 mmol/L NaCl, pH 7.4) in the presence of CaCl2 (5 mmol/L) and BSA (1 mg/mL; Sigma, St Louis, MO) for 5 minutes at 37°C. Then factor Va (1.2 nmol/L) was added to the incubation mixture to measure factor Va activity in a one-stage clotting time assay with factor V-deficient plasma. The amount of factor Va was determined with a calibration curve with purified factor Va. APC (34 pmol/L) in the presence or absence of protein S (3.4 nmol/L) was added to the incubation mixture, and after 5 minutes a sample from this mixture was taken and tested for residual factor Va activity. The average inactivation in 5 minutes was 480 pmol/L factor Va (40% of the added amount) in the absence of protein S. When protein S was present, 600 pmol/L factor Va was inactivated by APC in 5 minutes. The effect of patient IgG on the APC-mediated factor Va inactivation was tested in at least five independent experiments.

Adsorption of aPL

Cardiolipin (CL) vesicles were prepared according to the method described by Pengo et al.39 with some modifications. In short, CL (Sigma) was dried under a stream of nitrogen and resuspended to a concentration of 6 mg/mL in TBS by vigorous agitation using a vortex mixer. IgG (21 mg/mL) and CaCl2 (5 mmol/L) in the presence or absence of APC (102 pmol/L), protein S (10.2 nmol/L), prothrombin (3 μmol/L), β2-GPI (4.8 μmol/L), factor Va (71.1 pmol/L), or factor Xa (1.5 mmol/L) were incubated with the CL vesicle suspension (0.6 mg/mL) for 15 to 90 minutes at room temperature. After centrifugation at 80,000g for 20 minutes, the supernatant containing non-adsorbed IgG was collected and stored at −20°C.

RESULTS

Effect of IgG on EC-Mediated Prothrombinase Activity

The effect of IgG fractions from 30 different patients on the prothrombinase activity on EC was investigated (Table I). Control and patient IgG (7 mg/mL) was preincubated on EC monolayers and, after 60 minutes of incubation, prothrombin, factor Va, and factor Xa were added. After 45 minutes, the amount of generated thrombin was determined. Of the 30 patient IgGs tested, 4 (nos. 1, 2, 15, and 18) inhibited the EC-mediated prothrombinase activity (Fig 1 and Table 1) compared with the results with control IgG. The same inhibition was found when patient IgG was added simultaneously with the clotting factors (not shown). Increasing the IgG concentration (up to 10 mg/mL) and varying the IgG incubation time (from 15 up to 60 minutes) did not influence the results (not shown).

Effect of IgG on Factor Va Inactivation by APC

The effect of IgG fractions from 30 patients on the factor Va inactivation by APC was investigated in the presence of cephalin (Table I). Control and patient IgG (7 mg/mL) was preincubated with cephalin for 5 minutes and the capacity of APC to inactive factor Va was estimated. From the 30 different patient IgGs, 3 IgGs (nos. 1, 2, and 9) inhibited factor Va inactivation by APC significantly (Fig 2A and Table 1) compared with the results of control IgG. For all 3 inhibiting IgGs, a maximal inhibition was found with 7 mg/mL IgG (data not shown). These APC-inhibiting IgGs also inhibited the effect of protein C on the EC-mediated prothrombinase activity (not shown), indicating that this APC-inhibiting effect is independent of the phospholipid source used (cephalin or EC).

Effect of IgG on Factor Va Inactivation by APC in the Presence of Protein S

The effect of IgG fractions from 30 patients on the factor Va inactivation by APC and protein S was studied in the presence of cephalin. Cephalin was preincubated for 5 minutes with control and patient IgG (7 mg/mL). After the addition of factor Va, APC, and protein S, the amount of factor Va inactivation in 5 minutes was determined. Seven IgGs (nos. 1, 2, 3, 9, 10, 18, and 28), including the 3 IgGs that inhibited APC activity in the absence of protein S, inhibited factor Va inactivation in the presence of protein S significantly (Fig 2B and Table 1) compared with the results obtained with control IgG.
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Fig 1. Effect of patient IgG on EC-mediated prothrombinase activity. EC were preincubated with IgG from controls or patients and the EC-mediated prothrombinase activity was determined by measuring thrombin generation. Results ± SD were expressed as a percentage of the results obtained with control IgG (100% = 150 mmol/L IIa). The normal range of results with control IgG (mean ± 2 SD) is indicated by the horizontal lines.

Characterization of the Specificity of IgGs That Inhibit the Prothrombinase and Factor Va Inactivation Assays

To characterize the specificity of the patient IgGs that inhibited prothrombinase and APC activity, the purified IgGs were incubated with CL vesicles. Ca²⁺ (5 mmol/L) was added to the vesicles to ensure that CL was in the hexagonal II phase. After centrifugation, the supernatants containing nonadsorbed IgG were tested again in the same assays.

Prothrombinase activity. The specificity of IgG that inhibited prothrombinase activity from patients no. 1, 2, and 15 and IgG from patient no. 9 as a noninhibiting control was characterized.

When IgG was incubated with CL vesicles alone, no prothrombinase inhibitory activity could be adsorbed from the IgG solution in 30 minutes (Fig 3). When purified prothrombin was added to the CL vesicles, the prothrombinase inhibitory activity could be adsorbed from the IgG solutions (Fig 3). The addition of β2-GPI, APC, factor Va, or factor Xa to the vesicles had no effect. CL vesicle incubations, in general, had no effect on noninhibiting IgG from patient no. 9 (Fig 3A).

IgG from patients no. 1 and 2 prolonged the aPTT of normal plasma (1:1 diluted with buffer; 122 seconds) 40 and 67 seconds, respectively. After adsorption of prothrombinase-inhibiting patient IgG, the supernatant prolonged the aPTT of normal plasma only 30 and 27 seconds, respectively (10 and 40 seconds less prolongation after adsorption), but did not become normal.

From the 4 prothrombinase-inhibiting IgGs (nos. 1, 2, 15, and 18), 2 (nos. 1 and 15) also reacted with prothrombin coated to ELISA wells (in the absence and presence of CL), although binding strongly increased in the presence of CL. Prothrombin in solution did not compete with coated prothrombin for binding of IgG, indicating that the binding is specific for prothrombin bound either to ELISA plates or to CL (data not shown).

APC activity. The specificity of IgG that inhibited APC activity from patients no. 1, 2, and 18 and control IgG was characterized.

Incubation of IgG that inhibited APC activity with CL vesicles alone (15 minutes) had no effect on the APC-mediated factor Va inactivation (Fig 4). Only after prolonged incubation (90 minutes) were the CL vesicles able to adsorb the inhibitory activity (not shown). When purified APC was added to the CL vesicles, the APC-inhibitory activity could be adsorbed from IgG solutions of patients no. 1 and 2 within 15 minutes (Fig 4). When APC and protein S were added to the CL vesicles, the APC- and protein S-inhibitory activity could be adsorbed from the IgG of patient no. 18 (Fig 4).

After adsorption, the supernatants of all these vesicle incubations remained positive in the aCL ELISA and prolonged the aPTT of normal plasma to the same extent as the IgG before vesicle adsorption. IgG that inhibited APC activity did not react with protein C or S alone when tested in an ELISA system with coated protein C or S.

DISCUSSION

Although many possible pathophysiologic mechanisms of aPL have been investigated, a general mechanism that explains how aPL cause thrombosis has not been found. Furthermore, the paradoxical association between the presence of antibodies prolonging phospholipid-dependent clotting tests in vitro (LAC) and the occurrence of thrombotic complications in vivo has not been elucidated.

From the 22 IgG fractions that prolong the aPTT of normal plasma, only 4 (18%, Fig 1) could inhibit the prothrombinase activity on endothelial cells. This suggests that in most patients with LAC the prolongation of clotting tests is an in vitro phenomenon. A positive LAC test is probably caused by antibody-mediated agglutination of phospholipids in suspension, thereby limiting the surface available for coagulation reactions. This reaction is frequently dependent on the pres-
ence of β2-GPI.\textsuperscript{13} When a more physiologic surface such as EC is used for the assembly of the prothrombinase complex, the agglutination of phospholipids cannot take place. Furthermore, we showed that the antibodies that do inhibit the prothrombinase activity under these conditions exert their action via binding to phospholipid-bound prothrombin (Fig 3), as already suggested by others.\textsuperscript{12} This limits the amount of prothrombin available for the prothrombinase complex. So, the commonly accepted idea that the antibodies bind to phospholipids, thereby preventing binding of coagulation factors to phospholipids, is unlikely. Whether the thrombotic tendency of the 4 patients with IgG that inhibited prothrombinase activity can be explained by a decreased thrombin generation remains the question. Because thrombin has an anticoagulant as well as a procoagulant function, it is not clear what the effect of less thrombin will be. The new concept that aPL are directed to a combination of phospholipids and prothrombin prompted us to study whether complexes of phospholipids and other phospholipid-binding coagulation proteins than prothrombin could be epitopes for aPL. The anticoagulant proteins protein C and protein S seemed to be good candidates because interference of aPL with the function of these proteins could explain thrombotic tendencies. In addition, it has been reported that some aPL-positive IgG fractions could inhibit protein C activity, but the precise mode of action of aPL has not been elucidated.\textsuperscript{25,26}

The same population of 30 patients, of which 26 had aPL (LAC and or aCL) and 23 had a history of thrombotic c...
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3
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factor Xa,
or factor Va as indicated. The effect of untreated patient B2-GPI (82) as indicated.
was preincubated with CL vesicles containing prothrombin, APC,
was preincubated with CL vesicles containing prothrombin
on EC-mediated prothrombinase activity was determined. Results
were expressed as a percentage of the results obtained with un-
on EC-mediated prothrombinase activity was determined. Results
were expressed as a percentage of the results obtained with un-
treated control IgG (mean - 2 SD) is indicated by the horizontal line.

Fig 3. Effect of IgG adsorption by CL vesicles on EC-mediated
prothrombinase activity. (A) IgG from patients no. 15 (■) and 9 (□)
was preincubated with CL vesicles containing prothrombin (II) or
p2-GPI (p2) as indicated. (B) IgG from patients no. 1 (■) and 2 (□)
was preincubated with CL vesicles containing prothrombin, APC,
factor Xa, or factor Va as indicated. The effect of untreated patient
IgG and IgG not adsorbed with the vesicles (vesicle supernatants)
on EC-mediated prothrombinase activity was determined. Results
were expressed as a percentage of the results obtained with un-
treated control IgG. The lower level of the normal range of results
with control IgG (mean - 2 SD) is indicated by the horizontal line.

From the patient population studied, 23 had a history of
thrombotic complications, of which 7 had IgG that inhibited
APC activity, which might explain their thrombotic tendency.
The cause of thrombosis in the remaining 16 patients is as
yet unknown. Possible explanations are that thrombogenic
antibodies were not present in the IgG fraction, but in the
IgM or IgA fractions. Another possibility is that other phos-
pholipid-binding coagulation proteins can be part of the epi-
tope for subpopulations of aPL, such as tissue factor pathway
inhibitor or annexin V, which could lead to thrombosis. Fur-
thermore, it could not be excluded that the presence of these

Fig 4. Effect of IgG adsorption by CL vesicles on the APC-me-
diated factor Va inactivation. IgG from controls (■) and patients no.
1, 2, and 18 was preincubated with CL vesicles containing APC
and protein S (pS) as indicated. The effect of untreated patient IgG
and IgG not adsorbed to the vesicles (vesicle supernatants) on the
APC-mediated factor Va inactivation in the presence or absence
of protein S (as indicated) was determined. Results were expressed
as a percentage of the results obtained with untreated control IgG.
The lower level of the normal range of results with control IgG (mean
- 2 SD) is indicated by the horizontal line.

It was found that from the 30 patient
IgGs tested, 3 inhibited APC activity independent of the
presence of protein S and 4 additional IgGs inhibited when
protein S was also present (Fig 2). Of these 7 inhibiting IgG
fractions, 3 also inhibited prothrombinase activity. IgG that
inhibited APC activity could be adsorbed with CL vesicles
to which APC was bound. IgG that inhibited APC only in the
presence of protein S could be adsorbed with CL vesicles
to which APC and protein S was bound. No cross-reactivity
existed between IgG directed against the combination of
phospholipids and APC and IgG directed against the com-
bination of phospholipids and prothrombin (Fig 3B). These
results showed that in the autoantibody population of lupus
patients, there are antibodies that recognize CL and APC as
antigen, CL and APC and protein S as antigen, or CL and
prothrombin as antigen. Thus, the antigenic structures to
which aPL are directed are heterogeneous. In patients, dif-
ferent subpopulations of antibodies were present, and in some
patients more than one type of antibodies was present si-
multaneously. For example, patients no. 1 and 2 had anti-
bodies against phospholipids in combination with APC as
well as with prothrombin.

The antibodies that inhibited APC activity were distinct
from antibodies that inhibited prothrombinase activity and
aCL and LAC. Because deficiencies in protein C and S are
known to be associated with thrombotic complications, it is likely that antibodies directed against a combination of
phospholipids, APC, and protein S are responsible for the
thrombotic complications of these patients. This also suggests
that the commonly used aPL tests (aCL ELISA and LAC
test) do not detect the real pathogenic antibodies. Maybe this
can also explain the thrombotic complications of patients
with no detectable aPL. A good example is patient no. 28,
who had a history of recurrent thrombosis but no positive
aCL or LAC test. This patient had antibodies that inhibited
APC and protein S that might explain his thrombotic history.
These results indicate that it is important to develop more
accurate tests for the detection of autoantibodies causing
thrombosis.

From the patient population studied, 23 had a history of
thrombotic complications, of which 7 had IgG that inhibited
APC activity, which might explain their thrombotic tendency.
The cause of thrombosis in the remaining 16 patients is as
yet unknown. Possible explanations are that thrombogenic
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tope for subpopulations of aPL, such as tissue factor pathway
inhibitor or annexin V, which could lead to thrombosis. Fur-
thermore, it could not be excluded that the presence of these

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antibodies can be transient, resulting in an absence of thrombogenic antibodies in samples taken a long time after thrombotic episodes. Therefore, it would be of great interest to study patients retrospectively and prospectively using tests measuring thrombogenic antibodies rather than aPL in general.

After we finished this report, Vermolen and Arnout speculated on the varying affinities of aPL for complexes of phospholipids and phospholipid-binding proteins. They suggested classification of aPL on the basis of protein-phospholipid complexes with which they preferentially interact. Including this report, four different classes have been described (reacting with phospholipids and β2-GPI, prothrombin, protein C, and protein S) and one might expect that this number will increase in the near future, emphasizing the heterogeneity of the aPL population.

In conclusion, the heterogeneous manifestations of thrombosis in patients with aPL can probably be explained by a heterogeneous specificity of aPL for complexes of phospholipids and plasma proteins, leading to different thrombogenic mechanisms of aPL in patients.

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Antiphospholipid antibodies directed against a combination of phospholipids with prothrombin, protein C, or protein S: an explanation for their pathogenic mechanism? [see comments]

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