The antiphospholipid syndrome and heart valve surgery

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Summary

The antiphospholipid syndrome (APLS) is a complex autoimmune disease often connected to systemic lupus erythematos. Main features are thromboses, fetal loss and specific antibodies. The involved autoantibodies are directed against plasma proteins such as beta2glycoprotein1 (β2GPI) or prothrombin which depend on negatively charged phospholipids. Direct antibodies against phospholipids are of no importance for APLS. Clotting tests such as activated partial thromboplastin time or diluted Russell’s viper venom test (dRVVT) can show a prolonged time for coagulation despite a prothrombotic state in vivo but the investigator needs awareness about disturbing phospholipid sources and other influential factors. Enzyme linked immuno sorbent assay tests for antibodies against cardiolipin, β2GPI and prothrombin are valuable solid phase tests with different specificity. Antiphospholipid, anticardiolipin or lupus anticoagulant are misnomers in connection with APLS. They are preserved as a reminiscence of the pioneering work on the way to the still not exactly revealed basics of APLS. Valve operations in APLS patients seem to be rare; a meta-analysis of 57 cases proves that the perioperative management is, at the moment, an empirical approach with high morbidity and mortality in these young patients.

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1. Introduction

Antiphospholipid syndrome (APLS) [1] comprises clinical features such as arterial or venous thromboses or fetal loss and the detection of so-called antiphospholipid antibodies (aPL) as anticardiolipin antibodies (aCL) or lupus anticoagulant (LA). Many other symptoms such as thrombocytopenia, livedo reticularis, seizures, heart valve disease or insidious organ failure occur in APLS but are not sufficient by themselves to fit the actual classification criteria (Table 1).

To narrow the gap between recent research results and daily clinical practice this article briefly reviews the actual knowledge about APLS and the experience with APLS patients in heart valve surgery.

2. Historical notes — where the name of the syndrome comes from

Many of the terms used in literature and actually even the word ‘antiphospholipid’ in the name of the syndrome are rather misleading and should be mainly considered as reminiscence of the historical origin. For misleading or inaccurate terms we use quotation marks in this review.

The Wassermann reaction, having been used now for a 100 years, and later the Venereal Disease Research Laboratory test (VDRL) detected antibodies in patients with syphilis, which reacted against phospholipid structures. These antiphospholipid antibodies are induced by exposed phospholipids on the surface of treponema bacteria as a defence reaction in an infected patient. False-positive results in these tests were often related to systemic lupus erythematos (SLE) and other non-infectious autoimmune diseases [2].

In 1941 cardiolipin (CL) was detected as one specific target phospholipid for antibodies of syphilis or SLE sera [3] and became the basis for the VDRL test mixture [4]. Cardiolipin is one of several phospholipids (PL), ubiquitary and basic element of membranes in organisms. Negatively charged phospholipids such as CL or phosphatidylserine are mainly confined to the inner (cytoplasmatic) layer of bilayer cell membranes and to intracellular membranes. The outer contact layer of the cell membrane to the surrounding is
II. Laboratory criteria (positive test on two or more occasions at least 12 weeks apart, standardised procedures)

- b

Main target antigens beta2-Glycoprotein-1 (2GPI), Prothrombin, Annexin V

Other putative antigens Thrombin, protein C, protein S, thrombomodulin, tissue plasminogen activator, kininogens (high or low molecular), prekallikrein, factor VII/VIII, factor XI, factor XII, complement component C4, heparan sulfate proteoglycan, heparin, oxidised low-density lipoproteins

GPL: immunoglobulin G (IgG) anti-phospholipid units, MPL: immunoglobulin M (IgM) antiphospholipid units.

normally built up by neutral PL (e.g. phosphatidylcholine) [5,6].

The development of higher sensitive solid phase immunoassays (cardiolipin as antigen fixed on polystyrene plates) [7] to detect anticardiolipin antibodies and the correlation of positive tests with special clinical features as thromboses or recurrent fetal losses in some SLE patients led Hughes [8] to subgroup these patients and coined the term 'antiphospholipid syndrome' in 1985. Soon there were patients found with similar features but without SLE, then called primary APLS opposed to secondary APLS when combined with an autoimmune disease (e.g. SLE or rheumatoid arthritis).

Since 1990 [9,10] it has been known that the pathogenic antibodies responsible for the main symptoms of APLS are not (direct) aPL against phospholipids itself as produced in infections (e.g. syphilis), neoplastic disorders or induced by certain drugs (e.g. phenothiazines, quinidine) [11] but rather indirect aPL actually directed against certain phospholipid-depending proteins.

3. Etiology — phospholipids have to take the back seat

The formation of antibodies against foreign particles is an essential part of successful survival strategy in nature. When the human body is infected by viruses, bacteria or other membrane-covered particles one natural response is the forming of antibodies against structures on the surface (e.g. membrane proteins) or, after processing, against intracellular particles of the invader. Isolated phospholipids are not immunogenic but presented as part of a bigger structure as the membrane bilayer and especially when coupled to highly immunogenic adjuvants as lipid A (a glycolipidophospholipid and integral part of outer surface of gram negative bacteria) the induction of direct antiphospholipid antibodies is proven [12–14]. But be warned — direct antibodies against phospholipids, common after infections, seem to play no role in the antiphospholipid syndrome itself. However, they still cause a good amount of confusion in nomenclature and understanding.

The supposed targets of pathogenic antibodies in APLS are plasma or vascular cell proteins (Table 2). The main autoantigens are attracted to negatively charged phospholipids (PL−) [9] which are exposed on the outer side of cell membranes in a greater amount only under special circumstances such as damage or apoptosis (e.g. endothelial cell) or after activation (e.g. platelets).

The physiological function of beta-2-glycoprotein-1 (β2GPI), the putative main autoantigen in APLS, is still unknown. Prothrombin, another important autoantigen in APLS, is a well known part of the clotting cascade with anticoagulative properties (activation of Protein C) as well. Annexin V is a natural anticoagulant acting competitively for phospholipids against coagulation factors (inhibition of the prothrombinase complex). Anti-Annexin V-antibodies are found specifically in 50% of females with recurrent pregnancy loss [19] but are not further topics of this review.

Infective agents such as viruses (e.g. hepatitis-viruses, cytomegalovirus, varicella-zoster-virus) or bacteria (e.g. neisseria, treponema, mycoplasma pneumoniae, streptococcus pyogenes) are considered the most prominent trigger to induce the pathogenic APLS autoantibodies [20], but not by exposure of phospholipids. Several research groups [21–23] found striking similarities between amino acid sequences of proteins in infective agents and of target epitopes on human proteins as β2GPI. Simple cross reactivity due to antigenic similarity could lead to an autoimmune response as a 'mistake' of nature and is discussed as an important trigger for APLS. A genetic polymorphism could be an additional
variable favouring the molecular mimicry in a susceptible host [23,24].

4. Pathophysiological mechanisms —nothing is fact yet

4.1. Putative pathways for induction of thrombosis with involvement of β2GPI or prothrombin — a simplified theory for a complex problem

No single theory can explain the multitude of clinical findings and laboratory results summarised under the term APLS. The diversity of phospholipids, putative autoantigens and epitopes on these autoantigens is probably the cause for the variety of clinical symptoms and test reactivity. Potentially affected pathways leading to thrombosis include the direct activation of coagulation, the inhibition of anticoagulation and the interference with endothelial cells, immunocompetent cells or platelets (Table 3) [18,25,26].

The anticoagulant appearance in clotting tests in vitro and the hypercoagulative state of APLS-patients in vivo is one of the major puzzles in APLS. Recent research results reveal parts of this mystery at least for the best-investigated target autoantigens β2GPI and prothrombin.

- Beta-2-Glycoprotein-1 (β2GPI) — the big mystery

β2GPI, another name is apolipoprotein H, is a 50 kDa serum protein (phospholipid molecule <1 kDa, IgG about 144 kDa) with its coding gene on chromosome 2. The plasma concentration is about 150–300 μg/ml. It consists of 326 amino acids as a highly glycosylated single, J-shaped chain [27–29] and is organised in a 5 domain (so called ‘sushi’) structure. A cationic, lysine-rich binding site to negatively charged phospholipids (PL(C14) next to a hydrophobic insertion loop is the main functional part of domain 5. Binding sites for autoantibodies are found in all domains, some of these being strongly connected to the development of a hypercoagulative state in APLS [30]. Annexin II was identified as an endothelial cell membrane receptor with high affinity to β2GPI, also receptor (different site) and enhancer to tissue type plasminogen activator (t-PA) [31]. The physiological function of β2GPI is not yet revealed; proposed is some role in lipid metabolism [32], known features are the involvement in the clearance of apoptotic bodies from the circulation and some anticoagulative properties [28,33]. By reducing the uptake of oxidised LDL it may have a protective role in atherosclerosis [34].

Fig. 1. Model of transmembrane cell activation and inhibition processes by β2GPI/anti−β2GPI-complex (adapted from Rouhey and Hoffman [26] and de Groot and Derksen [51]); (1–8) Attraction of β2GPI/domain I-V to exposed negatively charged phospholipids, eventually resulting in a prothrombotic state if an autoantibody is bound; receptor 1 — transmembranic, e.g. toll-like-receptor 4 (TLR 4) on endothelial cell membranes [23], apolipoprotein-E-receptor-2’ (apoER2’) on platelets [36,37,38], fragment-constant-y-receptor II (FcγRII) on monocytes [39]; receptor 2 — nontransmembranic, e.g. annexin II [23]; t-PA — tissue type plasminogen activator (inhibition by displacement).
signal the expression of adhesion molecules as E-selectin, vascular-cell-adhesion-molecule-1 (VCAM-1) or intracellular-adhesion-molecule-1 (ICAM-1) increase the adhesion of immunocompetent cells further activating endothelial cells. Eventually the production of tissue factor or inhibition of tissue-factor-pathway-inhibitor (TFPI) activates the (extrinsic) coagulation pathway [40—44] and the decreased production of prostacyclin promotes vasoconstriction and platelet aggregation. The activation of platelets results in the production of thromboxane A2 with further platelet activation and increased adhesion to collagen or fibronectin [38]. The displacement of t-PA from annexin II receptor could reduce the plasmin activation and as consequence decelerate the fibrinolysis (step 5b in Fig. 1).

The increased affinity of $\beta2GPI/anti\beta2GPI$-complexes to $PL^{\text{(-)}}$ causes an increased and prolonged capturing of added $PL^{\text{(-)}}$ in clotting tests. This results in a reduced activation of $PL^{\text{(-)}}$ depending clotting factors and eventually prolongs the coagulation time; this is at least a reasonable theory to explain the puzzling lupus anticoagulant phenomenon (Fig. 2).

- Prothrombin (PT) — not a quite unexpected villain

PT, coagulation factor II, precursor of thrombin, is a 72 kDa plasma protein with its coding gene on chromosome 11. Produced in the liver, it is post-translationally modified in a vitamin K depending reaction that converts glutamic acid rests to gamma-carboxyglutamic acid rests. These modified amino acids are crucial for the binding of calcium ions ($Ca^{2+}$) and $PL^{\text{(-)}}$; each binding accompanied by conformational changes [45]. $Ca^{2+}$ and $PL^{\text{(-)}}$ are important cofactors for the first of the two-step cleavage of prothrombin into thrombin (36 kDa), splitting off fragment I (resulting in prothrombin as intermediate product) and fragment II. Splitting enzyme is the prothrombinase complex, consisting of the activated factors X and V. After binding of PT to $Ca^{2+}$ and $PL^{\text{(-)}}$ the antibody can attach to a previously hidden epitope on PT enhancing the affinity of PT to $PL^{\text{(-)}}$ [46,47]. The thrombin activation could be enhanced by accelerated splitting off prethrombin 1 from fragment I or the coagulation is overactivated by transmembrane signal processing as described for $\beta2GPI$. Alternatively or in addition autoantibodies to PT, thrombomodulin, Protein C or Protein S could inhibit the physiological anticoagulative properties of thrombin [16,17].

The prolongation of coagulation time in clotting tests can, as for $\beta2GPI$, be explained by the increased affinity of PT/antiPT-complexes to $PL^{\text{(-)}}$ leading to an increased capturing of $PL^{\text{(-)}}$ and a considerably postponed dissociation [48]. Due to the limited amount of added PL it results in a net decrease in fibrin formation even if the cleavage of PT into fragment I and prethrombin is enhanced.

Because bivalency of the antibody is necessary [48,49] only cross linkage of two prothrombin molecules by one antibody [50,51] or bivalent binding of one prothrombin molecule seem to result in a prothrombotic state in vivo and LA-effect in vitro.

Why do thrombotic events in APLS patients occur apparently only sporadically despite well-documented coexistence of autoantigens and its antibodies in blood over long periods?

1. Assuming a two-hit hypothesis, only if $PL^{\text{(-)}}$ in an unusual amount are exposed — (for example after endothelial cell damage) the above mentioned processes would be started [25,52]. The concentration of attracted autoantigens in high density and consecutive cross-linkage of autoantibodies is possibly the crucial step for transmembrane cell activation. Alternatively an acute infectious process could simultaneously activate special receptors (e.g. TLR) and synergistically with antigen/antibody-complexes overactivate the coagulation cascade [23]. The exposure of hidden epitopes, only if the autoantigen binds to $PL^{\text{(-)}}$, could explain the obvious coexistence of autoantigens and correlating autoantibodies in blood over long periods.

2. It can be assumed that thrombotic events actually happen much more often, but only in microvasculature or vessels of smaller size, causing an insidious deterioration of organ function such as renal failure, cerebral changes or impairment of the myocardial function by multiple recurrent microthromboses or microemboli, possibly not diagnosed as APLS.

4.2. A putative pathophysiological mechanism for heart valve involvement in APLS — the same theory with a specific target

Since the description by Libman and Sacks in 1924 a distinct noninfectious, inflammatory verrucous endocarditis of the heart valves preferred on the left side is known in patients with systemic lupus erythematoses. Noninfectious
and noninflammatory but rather thrombotic or fibrotic/calci
cific lesions were found in patients with primary APLS
[53—55]. Discussed is a autoimmunological mechanism
similar to the one for intravascular thrombosis. The
endocardium, particularly the surface of the left-sided
valves, is vulnerable to microinjuries because of stress, jet
effect and turbulence [56, 57]. Alternatively, infective agents
could cause not only the induction of autoantibodies by
molecular mimicry but also (possibly small) damage on the
surface of a heart valve [58]. Microinjuries expose PL\textsuperscript{−1} on
superficial valve structures or on endothelial cells of
intravalvular capillaries [55], β2GPI or other PL\textsuperscript{−1} depending
plasma proteins are attracted, autoantibodies bind to the
PL\textsuperscript{−1}-autoantigen complexes causing a transmembrane or
epimembrane cell activation and tiny spots of coagulation.
By transforming the resulting microthrombi into fibrictic
tissue [59] the valve changes are initiated and in a vicious
circle of structural deformity and functional failure (stenosis
or incompetence) the valve can deteriorate further.
APLS is combined with SLE in about 40% of all APLS patients
and therefore the changes of the heart valves can also be
called by a SLE specific mechanism. Non-autoimmunogenic
reasons for heart valve failure in APLS-patients are possible
as well.

5. Pitfalls of laboratory tests — too few recognise the
importance of absent phospholipids

An integral part or the definition ‘APLS’ is the positive
testing for lupus anticoagulant, anti-cardiolipin or anti-β2GPI
twice at least 12 weeks apart [1]. The double testing helps to
avoid the inclusion of patients with a transient reactivity by
direct antiphospholipid-antibodies due to infections or other

Coagulation tests to reveal a lupus anticoagulant effect
are activated partial thromboplastin time (aPTT), diluted
Russell’s viper venom test (dRVVT), taipan venom test,
textarin venom/ecarin venom clotting time ratio, kaolin
clotting time and tissue thromboplastin inhibition test [11].

Enzyme linked immuno sorbent assays (ELISAs) as solid
phase tests no longer use only cardiolipin but also more
specific antigens as β2GPI, prothrombin or phosphatidylser-
ine/prothrombin to detect the correlating autoantibodies.
The tests themselves are delicate and need careful
processing and interpretation [60]. A prolongation of PL-
depending clotting tests such as aPTT, usually an indication of
a bleeding tendency, is in APLS patients connected with a
high risk for thrombotic/thromboembolic events.

5.1. Lupus anticoagulant — the name barks up the
wrong tree

First suggested in 1957 the term was coined in 1972
by Feinstein and Rapaport [61]. As known today ‘lupus
anticoagulant’ is a misnomer for a group of various
phospholipid inhibitors, present often without underlying
SLE and in vivo connected not to bleeding but to thrombotic
complications. In this review we refer to LA as an effect or
phenomenon of a functional test and not as a name for
possibly many different agents including direct or indirect
‘antiphospholipid’ antibodies.

What does ‘LA positive’ mean?

Several clotting tests such as aPTT, dRVVT or prothrombin
time (PT) depend on both calcium and phospholipids for an
adequate activation of several clotting factors (Factor II, VII,
IX, X) [62]. If the measured time of clot forming after addition
of Ca\textsuperscript{2+} and PL\textsuperscript{−1} is prolonged, one of the possible reasons is
the presence of antibodies interacting directly or indirectly
with phospholipids (Fig. 2). If the clotting time is not
corrected by addition of normal plasma (mixing step —
corrects missing coagulation factors) but shows a normal-
isation by addition of an excessive amount of phospholipids
(confimation step by adding of e.g. activated, PL\textsuperscript{−1} rich
thrombocytes) the LA effect is considered ‘positive’ — the
‘antiphospholipid’ dependent inhibition of the coagulation
test proven.

Several points about LA testing should be kept in mind:

(a) A test for LA, considered highly sensitive but not very
specific regarding thromboembolic risk in APLS patients,
can only be valid and reliable if as many as possible
sources for phospholipids are removed before the test. In
the daily routine plasma for clotting tests is prepared by
centrifugation of a blood sample with 2000—4000 × g for
about 10—20 min, removing the cellular particles (red
and white blood cells). The smaller and lighter
thrombocytes stay mainly in the supernatant and
provide, especially if frozen and thawed, a rich source
of PL\textsuperscript{−1}. For the routine test procedure an excessive
amount of PL is without influence, but for all tests where
a phospholipid dependency shall be revealed an extra
spin of the supernatant (5 min at 10,000 × g) or a
filtration step (0.2 μm cellulose acetate syringe filter) is
indispensable to remove the platelets [11].

(b) aPTT as the first and easiest test for orientation is
provided by numerous manufacturers and differs
because of different ingredients considerably in its
sensitivity towards the LA effect. The activator, a
reagent to provide an excessive foreign surface (activa-
tion of intrinsic or contact pathway) can vary (e.g.
kaolin, silica, celite or ellagic acid), the phospholipid
source and composition can differ widely (several animal
or plant sources, batch-to-batch differences) and the
clot-detection method/instruments (photo-optical,
mechanical, manual) used by the investigator influence
the result [63].

(c) Similar to aPTT is the principle of the dRVVT. But the
direct activation of factor X by snake venom which in
turn activates prothrombin in a Ca\textsuperscript{2+} and PL\textsuperscript{−1} depending
reaction is one possible reason for different results
regarding LA compared to aPTT. At least both these tests
should always be performed when plasma is tested for an
LA-effect [1].

(d) Not only pathogenic antibodies of APLS prolong the tests.
The test interpretation always necessitates a careful
review of the patient’s medical history.

(e) The prothrombin time, routine test for the extrinsic or
tissue factor pathway of coagulation is depending on Ca\textsuperscript{2+}
and PL\textsuperscript{−1} in factor VII, X and II [62, 64]. The activator,
tissue thromboplastin, is extracted from animal tissues
and along the way PL are provided excessively. It makes this test useless for APLS diagnostics. Recently a modified test with an exact amount of recombinant TF and (synthetic) phospholipids became available and allows the detection of LA [11].

(f) Other clotting tests, most of them on the basis of snake venoms, are available and promising because of their independency of several disturbing variables but still not used wide spread due to lack of standardisation.

5.2. Solid phase assays — the big hope for more specific diagnostics

- Anti-cardiolipin test — the classic

After fixation of cardiolipin to microtiter plates and incubation with plasma or serum direct antibodies bind to CL and can be visualised, formerly by radioimmunoassay today with enzyme-linked anti-antibodies and colour reactions (Fig. 3B–B’). Because direct antibodies to CL are not pathogenic for APLS this group of antibodies has to be considered as differential diagnosis in a positive test result.

β2GPI-molecules from test plasma or/and buffer solution also bind to fixed CL. Autoantibodies, if present, can bind to β2GPI and become visualised by ELISA colour reaction as well (Fig. 3C–C’), often stronger reacting then direct anti-cardiolipin antibodies.

Where are the pitfalls of this test?

(a) The patient’s serum is one source of β2GPI. The buffer solution, often bovine serum, blocks background binding sites and deliberately provides β2GPI as well. The homology between bovine and human β2GPI is used to introduce an extra amount of target antigens. But homology does not mean identity and the test result can be influenced if a present human autoantibody (isotype IgM rather then IgG) is reacting exclusively with human β2GPI [65]. This makes the colour reaction less powerful and false-negative because the strength of reaction is important for the diagnosis of APLS — only moderate to high titer antibodies are considered as ‘positive aCL’ for APLS (classification criteria Table 1).

(b) As mentioned already for the LA-tests the plasma should be platelet depleted. Otherwise exposed PL−1 on the surface of activated platelets attract β2GPI and then autoantibodies bind to this ‘fluid’ PL−1-source. The complexes are washed away without binding reaction to the fixed CL on the plate surface.

(c) Because CL is only one of several negatively charged phospholipids it is possible to miss a few cases in which specific autoantibodies are reactive to β2GPI only when bound to another PL−1, e.g. phosphatidylserine.

(d) Other important methodological considerations are the quality of cardiolipin, the techniques of coating, the used buffer, the standardisation and quantitative calculation in IgG-antiphospholipid units (called GPL or GPU) or IgM-antiphospholipid units (MPL or MPU) because the clinical significance of low titer aCL is doubtful [11].

- Anti-β2GPI and anti-prothrombin ELISA tests — the new-comers

The fixation of one specific autoantigen on the plate enables the direct identification of a matching autoantibody if present in the tested plasma (Fig. 3E). This test is very specific but because of the variety of suggested autoantigens not very sensitive for APLS. The fixation of autoantigens on microtiter plates requires a special pretreatment of the plate with irradiation to charge the otherwise neutral surface [66]. Since 2006 the solid phase assay for antiβ2GPI is acknowledged as a single test sufficient to confirm the diagnosis of APLS [1]. ELISA tests for antiPT, with prothrombin directly fixed on a plate or via phosphatidylserine (antiPS-PT) add further information especially if tests for LA, aCL or anti-β2GPI are persistently negative [67].

Even if direct fixation of a target autoantigen to microtiter plates and application in a solid phase ELISA improves the specificity of APLS diagnostics it should be kept in mind that binding of these antigens to PL−1 in vivo or to an artificially charged surface in vitro is probably not identical and could introduce a new source of misinterpretation. Furthermore, the buffer used after fixation of the target antigen to the plate can influence the result [68] and a better standardisation of the tests is mandatory [15,69]. Given a good standardisation it could be debated if these tests have to be repeated for confirmation of the diagnosis APLS because they are (theoretically) not influenced by non-pathogenic antibodies, cancer or drugs.
6. Practical impact of APLS in heart valve surgery — we do need more education

6.1. Review of literature — not easy to reconcile

Besides cardiac symptoms resulting from either thromboses in microvasculature with insidious deterioration and heart failure or overt thromboses/emboli in microvasculature with acute myocardial infarction [70] there is an entity of young, predominantly female adults [54] with APLS and heart valve disease severely enough affected to need an operation. The valve can be affected because of an APLS-specific mechanism and/or as a result of another disease (e.g. SLE, post rheumatic) or condition (e.g. bicuspid valve [71]).

Even if the prevalence of ‘antiphospholipid’ antibodies is not uncommon (about 3% in normal population) APLS seems to be a rare syndrome but often with valve involvement. About 30–40% of patients with primary APLS and about 50–60% of patients with SLE and APLS show an affection of one or more valves most often on the left side [57, 59, 72–74]. So far only few valve operations in APLS patients are reported in literature emphasising the complex problems which can arise during the surgical treatment. With the increasing knowledge about APLS more patients are expected to be diagnosed in time and a consequent treatment of APLS could result in an increased life expectancy. Thus potentially an increasing number of APLS-patients will be seen by a cardiac surgeon for an operation [75] in future. In 1996 Bouillanne et al. [76] investigated a cohort of 89 consecutive patients referred for a heart valve operation excluding patients with infection, SLE and patients on aPL inducing drugs. They confirmed ‘aPL’ in 21% of the patients compared to 9% in a control group. Taking the medical history and the laboratory results together, 8% of the patients even fulfilled the formal criteria for APLS, undiagnosed when referred for the valve operation. No higher rate of complications occurred in the group with ‘aPL’. Regarding complications Ciocca [77] reported opposite results in a retrospective analysis of 19 patients with ‘antiphospholipid’ antibodies and cardiovascular procedures, 8 of them underwent heart valve operations. Twelve of the 19 patients (63%) died of complications related to surgical intervention.

To the best of our knowledge the only publication about a heart valve operation in a child with primary APLS [78] reports on a mitral valve anuloplasty at an age of 8 months, followed by a tricuspid valve replacement at an age of 16 months followed by multiple episodes of valve thrombosis despite continued anticoagulation with warfarin, aspirin and persantine, each episode successfully treated with thrombolysis. Only during a follow-up at age of 2.5 years the diagnosis of APLS was revealed and an autosomal dominant transmission from the maternal side (deep vein thrombosis) discussed.

Cases with APLS and valve operation are listed in Table 4, some more are mentioned in literature but without sufficient or available further information [53, 76, 77, 79–84], hidden unseparated as SLE patients [85–87] or declared APLS on basis of lab tests without clinical signs [88, 89]. Most of the papers are single case reports, the largest series with 10 patients was published by Berkun et al. [90].

Even if the overall number of operated patients is small and the data incomplete some tendencies are noteworthy from the meta-analysis in Table 5:

(a) The known female: male ratio of about 3:1 in patients with primary APLS is mirrored in the patients ratio with valve affection and operation. A gender-specific valve deteriorating mechanism thus seems unlikely. The overwhelming predominance of females with valve operations in secondary APLS (27:1) could be explained by a separate independent pathogenetic mechanism for valve destruction due to SLE, a disease with a gender predisposition for females of 9:1 [125] and known specific valve pathology of Libman-Sacks-Endocarditis.

(b) SLE is the only important concomitant autoimmune disease reported in valve patients with secondary APLS.

(c) A valve operation in patients with primary or secondary APLS is typically performed in the age group between 25 and 55 years.

(d) Thrombotic or thromboembolic events rather than fetal loss are the typical feature in medical history of APLS patients with valve disease. The heart valves could be the source for these events and/or independent target of a (recurrent) prothrombotic pathogenetic mechanism.

(e) One of the few major differences between patients with primary and secondary APLS in this analysis is the pattern of affected valves. In patients with primary APLS the aortic and mitral valve are equally often involved, in patients with secondary APLS the mitral valve shows a clear predominance (75%) possibly due to SLE with its preferred affection of the mitral valve.

(f) A bioprosthesis was implanted in about 40% of aortic valve operations despite the young age of these patients. In only one case the desire for a child is reported as indication. A mitral valve repair was tried in 50% of patients (5/10) with primary APLS but only in 15% (3/20) of secondary APLS.

(g) The mortality is high with 7% early deaths and 12% late deaths after a mean follow-up period of less than 3 years.

(h) The early and late morbidity with 16 and 27 major complications (valve related included) respectively is significant. Only 42% of the patients (9 out of 21 completely reported cases) had an uneventful short and long-term recovery. APLS-typical processes could be explanation for the majority of listed postoperative problems, especially for myocardial and cerebral complications and other overt thromboembolic events. The high proportion of valve-related complications in 11 patients (about 20%) is remarkable. Three patients with mitral valve prostheses (two mechanical, one biological [90, 100, 124]) died due to valve thromboses, one patient with an aortic valve homograft needed reoperation due to graft deterioration after only 15 months [90], the other homograft prosthesis showed recurrent thromboses treated with thrombolysis [71]. Two bioprostheses were replaced less then 10 years after operation [103, 110].

(i) The histological examination in the group of primary APLS showed that out of 12 available results there were 11 specimens with thrombi on the valve surface, 10 patients presented with thickening and fibrosis and in
Table 4

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>F/M</th>
<th>Age</th>
<th>Valve operation</th>
<th>Valve type</th>
<th>Autoimmune disease</th>
<th>Early outcome</th>
<th>Late outcome, follow up time</th>
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<td>2007</td>
<td>M</td>
<td>52</td>
<td>AVR + MVR repair</td>
<td>Mech</td>
<td>SLE + APLS (TE, FL)</td>
<td>Complicated</td>
<td>Uncomplicated 36 m p/o</td>
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<td>2006</td>
<td>F</td>
<td>25</td>
<td>MV repair</td>
<td>Mech</td>
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<td>Mech</td>
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<td>M</td>
<td>36</td>
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<td>Mech</td>
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<td>57</td>
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<tr>
<td>Galve et al. [72]</td>
<td>1992</td>
<td>M</td>
<td>50</td>
<td>AVR</td>
<td>Mech</td>
<td>SLE + APLS (TE)</td>
<td>Death</td>
<td>n/app</td>
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<td>Alvarez-Blanco et al. [119]</td>
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<td>42</td>
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<td>Mech</td>
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<td>Complicated 18 m p/o</td>
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<td>Complicated 36 m p/o</td>
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<td>Mech</td>
<td>SLE + APLS (TE, FL)</td>
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<td>Mech</td>
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<td>F</td>
<td>41</td>
<td>MVR</td>
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<td>SLE + APLS (TE)</td>
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<td>Mech</td>
<td>SLE + APLS (TE, RF)</td>
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<td>Niaz and Butany [110]</td>
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<td>F</td>
<td>32</td>
<td>AVR + root patch</td>
<td>Bio</td>
<td>SLE + APLS (TE)</td>
<td>Uncomplicated</td>
<td>n/p</td>
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<tr>
<td>Sakaguchi et al. [111]</td>
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<td>55</td>
<td>AVR</td>
<td>Mech</td>
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<td>Araki et al. [112]</td>
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<td>36</td>
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<td>Garcia-Torres et al. [55]</td>
<td>1996</td>
<td>F</td>
<td>32</td>
<td>AVR</td>
<td>Bio</td>
<td>SLE + APLS (TE)</td>
<td>Death</td>
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<td>Escalante et al. [114]</td>
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<td>F</td>
<td>41</td>
<td>AVR</td>
<td>Mech</td>
<td>SLE + APLS (TE)</td>
<td>Uncomplicated</td>
<td>n/p</td>
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<td>Noji et al. [115]</td>
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<td>MVR</td>
<td>Bio</td>
<td>SLE + APLS (TE, FL)</td>
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<td>39</td>
<td>MVR</td>
<td>Mech</td>
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<td>n/p</td>
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<td>Takahashi et al. [118]</td>
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<td>41</td>
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<td>Mech</td>
<td>SLE + APLS (TE)</td>
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<td>F</td>
<td>33</td>
<td>AVR</td>
<td>Mech</td>
<td>SLE + APLS (TE)</td>
<td>Death</td>
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<tr>
<td>Galve et al. [72]</td>
<td>1992</td>
<td>M</td>
<td>50</td>
<td>AVR</td>
<td>Mech</td>
<td>SLE + APLS (TE)</td>
<td>Death</td>
<td>n/app</td>
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<tr>
<td>Hachul et al. [121]</td>
<td>1992</td>
<td>F</td>
<td>49</td>
<td>AVR + MVR</td>
<td>Bio2</td>
<td>SLE + APLS (TE)</td>
<td>Uncomplicated</td>
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<tr>
<td>Ford et al. [124]</td>
<td>1988</td>
<td>F</td>
<td>40</td>
<td>MVR</td>
<td>Bio</td>
<td>SLE + APLS (TE)</td>
<td>Uncomplicated</td>
<td>n/p</td>
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<tr>
<td>Ford et al. [124]</td>
<td>1988</td>
<td>F</td>
<td>20</td>
<td>MVR</td>
<td>Bio</td>
<td>SLE + APLS (TE)</td>
<td>Death</td>
<td>n/app</td>
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</table>


five patients there was (only mild) inflammation. Less thrombotic lesions and thickening/fibrosis but more samples with signs of inflammation were the typical findings in patients with APLS and SLE. These results support the assumption that a specific mechanism is responsible for valve disease in APLS patients but that comorbidities (SLE) or past diseases can cause relevant valve changes in APLS patients as well.
Table 5
Comparison between primary and secondary APLS in heart valve surgery patients (meta-analysis from Table 4)

<table>
<thead>
<tr>
<th></th>
<th>Primary APLS</th>
<th>Secondary APLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>29 (22:7)</td>
<td>28 (27:1)</td>
</tr>
<tr>
<td>(female/male)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (female/male)</td>
<td>42 (41/45)</td>
<td>41 (42/29)</td>
</tr>
<tr>
<td>Range age female/male</td>
<td>25–73/36–55</td>
<td>20–57/29</td>
</tr>
<tr>
<td>Main clinical signs of APLS:</td>
<td>FL/TE/FL + TE/rp</td>
<td>3/15/8/3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/16/7/3</td>
</tr>
<tr>
<td>Other reported autoimmune disease</td>
<td>SLE</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rheumatic fever in childhood</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>HIT II</td>
<td>1</td>
</tr>
<tr>
<td>Affected valve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TV/MV/MV + TV</td>
<td>13/21/1</td>
<td>4/21/1</td>
</tr>
<tr>
<td>Type of valve operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV (mech/bio/homog/unknown)</td>
<td>5/6/2/2</td>
<td>3/10/2/1</td>
</tr>
<tr>
<td>MV (mech/bio/repair/unknown)</td>
<td>4/15/16/4</td>
<td>12/5/3/4</td>
</tr>
<tr>
<td>TV (repair/rp)</td>
<td>0/1</td>
<td>2/0</td>
</tr>
<tr>
<td>Deaths (‘early’/‘late’)</td>
<td>6 (2/4)</td>
<td>5 (2/3)</td>
</tr>
</tbody>
</table>

6.2. Discussion — How can we improve the outcome for patients with APLS in heart valve surgery?

- Medical history and laboratory tests — do not miss the basics

Not always is APLS an established diagnosis when the patient is referred to the cardiac surgeon. A thrombotic/thromboembolic event in younger patients (< 55 years) or unclear pregnancy problems in females, other symptoms (e.g. livedo reticularis, renal failure, neurological/psychiatric symptoms) and/or a known SLE should prompt the search for 'antiphospholipid' antibodies preoperatively. Other possible reasons for a hypercoagulative state (Levine et al. [62]) have to be excluded by appropriate testing. Several tests for APLS antibodies should be performed and repeated in at least 12-week interval — if possible before the operation. Unfortunately even the absence of any positive result does not exclude the diagnosis of APLS completely because some autoantibodies are still only detectable in experimental laboratories.

The routine blood tests should be searched especially for spontaneously prolonged clotting tests (LA effect in aPTT, if suspicious repeated with specific request for LA testing), thrombocytopenia (possibly autoimmunological clearance or consumption) or signs of renal failure (recurrent insidious microthrombotic events) before surgery.

- Echocardiography — differentiation of underlying pathology is difficult

About 50% of APLS patients present with secondary APLS most often in combination with SLE or with postrheumatic and other reasons for valve changes. An infectious endocarditis showing similar pictures in echocardiography has to be excluded.

A pure ‘antiphospholipid’-antibody associated valve disease, according to the actual consensus committee proposal [1], is the echocardiographic detection of regurgitation (at least moderate for mitral valve) and/or stenosis of aortic and/or mitral valve in patients with ‘antiphospholipid’ antibodies. The defining lesions include valve thickness of more than 3 mm involving the leaflet’s proximal or middle portion and/or irregular nodules on the atrial face of the edge of the mitral valve and/or the vascular face of the aortic valve.

Calcification and chordal thickening (mitral valve), a common finding in postrheumatic valve changes, is described as rather rare and minimal [73], but the meta-analysis proves otherwise at least for patients with valve changes severe enough to need an operation.

- Coronary angiography — is mandatory despite the young age

Each patient with suspected APLS should undergo a coronary angiography with emphasis not only to overt lesions in the major coronary vessels but also to a possible rarefication of the end branches as sign of recurrent microemboli. An impairment of the left ventricular function could be valve related, caused by (recurrent) myocardial...
ischaemia/infarction, or sign of a direct autoimmunological involvement of the myocardium when SLE is present.

- Intraoperative management of coagulation — a crucial problem without clear solution

Because every clotting test result can be potentially misleading a scrutinised clinical judgement is mandatory. The use of the heart-lung machine in valve operations activates a bunch of immunological and coagulation responses and provides, by blood cell destruction, a rich source of negatively charged phospholipids as putative targets for the depending plasma proteins and their antibodies in patients with APLS. It makes the management of these patients challenging. Using heparin and protamine in the routine fashion is one of the options [52,96] and unavoidable if APLS is not known before the operation. The following anticoagulation regimens are described in literature and tried to improve the safety for the patient during and after CPB:

(a) Administration of at least as much heparin as usual, add extra doses to double the baseline ACT [113] or to reach an ACT twice the upper limit of normal [101].

(b) Preoperative titration of the ACT response to different doses of heparin in a sample of the patients blood, adjust the dose of heparin to be given according to the established target ACT (assuming a heparin concentration of $>3$ U/ml blood sufficient for an effective anticoagulation during CPB) [105].

(c) Use of other anticoagulants as bivalirudin in an empirical dose and without option of antagonisation if heparin antibodies are known [91].

(d) Use of other tests (factor Xa-level) to check the heparin action. This is unfortunately time consuming and thus not suitable for a quick check intraoperatively [105].

(e) Application of less protamine, e.g. by giving half of the calculated dose or no protamine at all [95,98,99,113,126].

All these attempts were performed on an empirical base by individual decision of the clinicians involved (team of surgeons, anaesthesiologists, haematologists). In our opinion more heparin than routine can and should be given to prolong the baseline ACT at least twice or above the routinely used target ACT (e.g. 400 s). Protamine to antagonise heparin should be administered only in a stepwise manner or in low dose continuously intravenous, e.g. 50 mg/h [113] until the bleeding tendency slows down to an acceptable amount. Of uppermost importance is a scrutinised operative technique and haemostasis to avoid any unnecessary surgical bleeding site.

- Which valve should be chosen? — An undecided question due to lacking long-term results.

The rather young age of the patients and the most often necessary long-term anticoagulation for APLS seem to make a mechanical valve the first choice if a replacement becomes necessary. But thromboembolic complications even with an INR of 3–4 puts a mechanical valve in danger of dysfunction with its sensitive hinge mechanism. Several authors [84,90,116,124] described valve related complications as thromboses and fatal outcomes.

The advantage of a bioprosthesis is the independence from complex monitoring of oral anticoagulation [106] but the only two reported long-term results (> 5 years) [103,110] documented valve failure and exchange after 8 and 9 years respectively not because of valve destruction but rather due to excessive pannus and consecutive stenosis.

Early destruction or thromboses of homograft valves are described and APLS-autoantibodies are discussed as being causative [90].

The mitral valve is the most often affected valve and reconstructive methods are in general first choice whenever possible, not only for insufficient but also for some stenotic valves. Should a valve in APLS patients, possibly direct target to autoantibodies, be preserved by reconstruction whenever possible? The reported early results (Table 4) are promising but long-term results are far too few to recommend this procedure as first choice. If sterile vegetations with thromboembolic complications in a structural and functional otherwise normal valve are the indication for operation a debridement and preservation of the valve is possible (personal experience R.Stanbridge,94). This is in contrast to bacterial endocarditis with the need for thoroughly removing all infected tissue.

Medical treatment with corticosteroids and anticoagulants as well as optimal therapy of congestive heart failure (e.g. diuretics, ACE-inhibitors) in four patients with thickened mitral valves and severe regurgitation was reported by Nesher et al. [73] as a successful alternative to an operation. Other authors deny an improvement of the valve pathology with steroid therapy or a disappearance of vegetations solely with anticoagulant/antithrombotic therapy [75].

- Postoperative management — severe problems often begin only now

The postoperative care should manage carefully the anticoagulation and be aware of each single organ failure or of a more complex complication, the catastrophic APLS (cAPLS). cAPLS is an acute condition with multiple vascular occlusions resulting in failure of several organ systems simultaneously or over a short period of time (days to weeks) [127]. It can be triggered by surgery, has a mortality of 50% and can resemble syndromes such as heparin-induced thrombocytopenia (HIT), disseminated intravascular coagulation (DIC), systemic inflammatory response syndrome (SIRS), SLE vasculitis, thrombotic thrombocytopenic purpura (TTP) or sepsis.

Differentiation between these severe complications is crucial and can be difficult. Only a good case history and established ‘antiphospholipid’ antibodies can give a hint to cAPLS. The reason for cAPLS is a generalised thrombotic activity (storm) due to excessive activation of ‘aPL’ with consecutive multi organ failure and peripheral ischaemic lesions (e.g. digital necrosis).

Besides an organ-specific therapy the treatment of cAPLS is opposite to some of the other mentioned syndromes (e.g. TTP, HIT). The baseline is an aggressive intravenous anticoagulation, usually heparin, later followed by oral anticoagulation with vitamin K-antagonists. Steroids, in order to limit the cytokine release and to treat the widespread vasculitis which mimics the cAPLS [128], and plasmapheresis
or intravenous gammaglobulins in order to reduce the anticoagulant load, improve the outcome [88,129]. The application of cytotoxic drugs, dialysis, fibrinolytics, splenectomy or prostacyclin are described but so far without proven advantage for survival.

Acute single organ failures (e.g. acute heart failure) where an APLS specific mechanism is supposed should be treated similar to CAPLS.

The symptomatic treatment, mainly the avoidance of thromboembolic complications by careful anticoagulative treatment, is so far the only long-term treatment option for APLS patients with valve replacement. The decision about the long-term anticoagulation depends basically on the medical history and chosen valve type. A lifelong anticoagulation with a vitamin K-antagonist (warfarin) is recommended after recurrent thromboses. The INR target should be rather high, at about 2.5—3.5, but no clear-cut data support this recommendation [58,131—132]. For APLS-patients with a valve repair or replacement this recommendation should be applied to every patient without severe contraindications to reduce the increased risk for valve related thrombotic or thromboembolic complications. Other risk factors for thrombosis should be treated optimally (e.g. hypertension, diabetes mellitus, hyperlipidaemia) or avoided (e.g. smoking) [133].

If further thrombotic events occur despite adequate anticoagulation the dose of warfarin and target INR can be increased and/or a platelet inhibitor added.

A therapeutic treatment for APLS is not available yet. One of several approaches is, the application of peptides specifically bound by anti-β2GPI antibodies thus neutralising the functional effect of the autoantibodies [134]. Another experimental attempt is the treatment with peptides which have a similar amino acid sequence as domain V of β2GPI thus possibly blocking putative receptors in an antagonistic manner [135].

7. Summary

The antiphospholipid syndrome is a complex autoimmune disease, often connected to systemic lupus erythematoses. Main features are thromboses, fetal loss and specific antibodies. The involved autoantibodies are directed against plasma proteins as β2GPI or prothrombin which depend on negatively charged phospholipids. Direct antibodies against phospholipids are without importance for APLS. Clotting tests such as aPTT or DRVVT show a prolonged time for coagulation despite a prothrombotic state in vivo but the investigator needs to be aware about disturbing phospholipid sources and other influential factors. ELISA tests for aCL, antiβ2GPI and antiIgG are valuable solid phase tests with different specificity. 'Antiphospholipid', 'anticardiolipin' or 'lupus anticoagulant' are misnomers in connection with APLS. They are preserved as reminiscence of the pioneering work on the way to the still not exactly revealed basics of APLS. Valve operations in APLS patients seem to be rare, a meta-analysis of 57 cases proves that the perioperative management is an empirical approach with high morbidity and mortality in these young patients.

8. Conclusions

(a) More reliable and specific tests should become available for an exact confirmation of APLS to improve the correlation of specific autoantibodies with specific clinical symptoms.

(b) Testing for APLS should be included in the thrombophilia screening for every younger cardiac patient with a history of thrombotic/thromboembolic events including acute myocardial infarction, chronic heart failure of unclear origin, early stent or coronary graft occlusion or thrombosis of a native or prosthetic heart valve.

(c) More reliable, easier and quicker coagulation tests should become available to manage the anticoagulation regimen in daily practice and under special circumstances like cardiac surgery.

(d) The further detection of pathophysiological mechanisms could provide treatment options tackling not only the symptoms of APLS but interfering directly with the binding cascade phospholipid-(plasma) protein-antibody.

(e) Because of the powerful in vivo activation mechanisms of coagulation under special circumstances, the extreme is the catastrophic APLS, the application as a treatment option in haemorrhagic disorders should be investigated as soon as the underlying mechanism is fully understood.

(f) Because of the limited experience with APLS patients in cardiac operations, especially valve operations, an international register should be initiated summarising the experience to improve eventually the short and long-term results of these high-risk operations.

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References


