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КЛАПАННАЯ БОЛЕЗНЬ СЕРДЦА ПРИ АНТИФОСФОЛИПИДНОМ СИНДРОМЕ (ОБЗОР ЛИТЕРАТУРЫ)

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Valvular Heart Disease In Antiphospholipid Syndrome (Review)

Резюме

Обзор посвящен особенностям клапанной болезни сердца (КБС) при антифосфолипидном синдроме (АФС). Кроме эпидемиологических данных и классификационных критериев АФС, приводятся сведения о распространенности, патогенетических механизмах, патоморфологических особенностях КБС, которая характеризуется веррукозным эндокардитом (или эндокардитом Либмана-Сакса), утолщением створок и дисфункцией клапанов. Основные патогенетические события КБС обусловлены воздействием антифосфолипидных антител, локальной агрегацией тромбоцитов, миграцией воспалительных клеток и отложением иммунных комплексов. Течение КБС при АФС нередко осложняется тромбоэмболическими осложнениями, включая эмболизацию артерий головного мозга и коронарных артерий. Диагностика КБС при АФС основывается на результатах эхокардиографии (ЭхоКГ), что позволяет выявить утолщение створок, веррукозные образования и оценить функцию клапанного аппарата. Использование чреспищеводной ЭхоКГ позволяет уточнить особенности клапанного поражения при неубедительных результатах трансторакальной ЭхоКГ. Обсуждаются вопросы ведения больных с АФС, имеющих КБС, с оценкой результатов применения антитромбоцитарной, антикоагулянтной, иммуносупрессивной терапии и хирургической коррекции выраженной клапанной патологии. Выполнение кардиохирургических вмешательств ассоциируется с повышенным риском развития послеоперационных осложнений, обусловленных кровотечениями или тромбозом, а также смертности.

Ключевые слова: *антифосфолипидный синдром, клапанная болезнь сердца, эндокардит Либмана-Сакса, вальвулит, эхокардиография, лечение, тромбоэмболические осложнения*

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Abstract

The review concerns special aspects of valvular heart disease (VHD) in antiphospholipid syndrome (APS). In addition to epidemiological data and classification criteria for APS, information is provided on the prevalence, pathogenetic mechanisms, and pathomorphological features of VHD, which is characterized by verrucous endocarditis (or Libman-Sacks endocarditis), thickening of the leaflets and valve dysfunction. The main pathogenetic events of VHD are caused by the effects of antiphospholipid antibodies, local platelet aggregation, migration of inflammatory cells and deposition of immune complexes. The course of VHD in APS is often complicated by thromboembolic complications, including embolization of the cerebral arteries and coronary arteries. Diagnosis of VHD in APS is based primary on the results of echocardiography, which allows to identify leaflet thickening, verrucous vegetations and assess the function of the valve apparatus. The use of transesophageal echocardiography makes it possible to clarify the features of valvular lesions in case of inconclusive results of transthoracic echocardiography. The issues of management of patients with and VHD are discussed, with an assessment of the results of the use of antiplatelet, anticoagulant, immunosuppressive therapy and surgical correction of severe valvular pathology. Cardiac surgery is associated with an increased risk of postoperative complications due to bleeding or thrombosis, as well as mortality.

Key words: *antiphospholipid syndrome, valvular heart disease, Libman-Sacks endocarditis, valvulitis, echocardiography, treatment, thromboembolic complications*

Conflict of interests

Co-author of the article Ignatenko G.A. is a member of the editorial council of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Ignatenko G.A. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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APS — antiphospholipid syndrome, aPLA — anti-phospholipid antibody, aCA — anti-cardiolipin antibody, anti-β_2GP1 — anti-β_2-glucoprotein 1 antibodies, LAC — lupus anticoagulant, SLE — systemic lupus erythematosus, CVD — cardiac valve disease, ACR — American College of Rheumatology, EULAR — European League Against Rheumatism, echoCG — echocardiography, MV — mitral valve, AV — aortic valve, TV — tricuspid valve, LSE — Libman-Sacks endocarditis, IE — infective endocarditis, TEC — thromboembolic complication, TTE — transthoracic echoCG, TEE — transesophageal echoCG, nBTE — non-bacterial thrombotic endocarditis, ACT — anticoagulant therapy, HCQ — hydroxychloroquine, GC — glucocorticoids

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease associated with venous, arterial or microvascular blood-clotting and/or complication of pregnancy, with laboratory evidence of persistent antiphospholipid antibodies (aPLA), such as anti-cardiolipin antibody (aCA), anti-β_2-glucoprotein 1 (β_2GP1) antibodies) and lupus anticoagulant (LAC) [1, 2].

APS can be primary, when the patient does not have signs of any disease, or secondary to another patholofy, e.g. an autoimmune disease (mostly systemic lupus erythematosus (SLE), neologisms and drug administration. APS can complicate the course of various infectious diseases, including coronavirus infection (COVID-19) [1, 3, 4].

According to a meta-analysis, the morbidity and incidence of APS are 1–2 cases per 100,000 and 40–50 cases per 100,000, respectively [4, 5]. APS is the leading cause of strokes in young patients, 33 % of strokes in patients below 50 years of age, and 20 % cases of recurrent miscarriages [6].

APS can be associated with involvement of almost any organ, mostly due to thrombotic and atherosclerotic processes [1, 2, 7]. A cardiac pathology in patients with APS significantly affects the clinical presentation, course, prognosis of the disease, and often results in severe complications and death. Cardiac pathologies in patients with APS are versatile and include cardiac valve disease (CVD), thrombotic and atherosclerotic coronary occlusion, ventricular dysfunction and dilatation, intracardiac thrombosis, and pulmonary hypertension [8, 9]. This review presents the data on the incidence, pathogenesis, pathomorphology, diagnosis, and current therapies of CVD in APS patients. Literature sources were searched in RSCI (Russian Science Citation Index), eLibrary, PubMed using keywords. The review includes articles

both in Russian and English, which were published over the period from 2014 to 2024. The analysis also included fundamental researches, which were conducted earlier, but which are highly valuable for this topic. Keywords for the literature search: antiphospholipid syndrome, cardiac valve disease, Libman-Sacks endocarditis, valvulitis, echocardiography, treatment, thromboembolic complications, events. The focus was on the articles published in scientific journals and peer reviewed.

Antiphospholipid syndrome diagnosis

There are currently no proper diagnostic criteria for APS; however, classification criteria developed mostly for clinical and interdisciplinary studies to identify homogenous groups are widely used [10, 11]. APS classification criteria usually include its most specific manifestations: arterial, venous thrombosis, microvascular thrombosis, miscarriage in patients with aPLA. In additional to laboratory findings, in each case APS is diagnosed based on a set of all clinical parameters, taking into account also non-specific manifestations of the disease[12]. Therefore, in clinical settings, APS classification criteria are used mostly for justification and confirmation of the diagnosis [12, 13].

The first classification criteria were proposed after the VIII International APS Congress, which was held in Sapporo (Japan) in 1998. During their discussion, the working group experts noted that although some clinical manifestations of APS (particularly low platelet count, haemolytic anaemia, *livedo reticularis*, CVD) are sometimes associated with APS, they do not demonstrate strong associations as signs included into the proposed classification criteria. During a separate workshop to discuss APS criteria held in November 2004 as part of the International APS Congress in Sydney (Australia), new criteria were proposed, which differed from the previous Sapporo wording of the laboratory criteria [14]. Moreover, experts proposed the wording for clinical manifestations, including CVD, which were not included into the classification criteria, but were useful for the diagnostics in some patients as possible, non-critical signs of APS or APS-associated characteristics [15].

The classification criteria developed by the American College of Rheumatology (ACR) together with the European League Against Rheumatism (EULAR) were published in 2023. They were based on the current idea of APS, which allowed weighing individual criteria, with exceptional performance characteristics and possible specificity of criteria [2] (Table 1).

It is worth mentioning that the 5th clinical domain is represented by CVD variants: thickened valve leaflets and/or valve vegetation, having relatively high weight — 2 and 4 points, respectively.

As compared to the 2006 Sydney criteria, 2023 ACR/EULAR criteria had a modified CVD definition [2, 14] (Table 2). The latest criteria describe age-related leaflet thickness; vegetation description is revised: vegetation can be villous, lobulated or round; and the most common size (< 1 cm) is mentioned. It is also noted that vegetations can be found not only on the mitral valve (MV) and aortal valve (AV), but also on any side of any valve leaflet.

Characteristics of cardiac valve disease in patients with antiphospholipid syndrome

CVD is the most common cardiac pathology in patients with APS, which affects approximately one third of patients. In patients with primary or secondary APS, changes in the endocardium are mostly thickened valve leaflets and vegetations. MV is the most common location (33.3–88.8 % of cases), followed by AV (13.1–51.3 %), tricuspid valve (TV) (3–12 %) and pulmonic valve (1 %) [15-22]. The causes of a higher incidence of left-side valve involvement include higher susceptibility of the endothelium to microdamage due to shear stress and higher loads at systolic blood expulsion from the left ventricle [23].

Generally, valve insufficiency prevails over stenosis and is usually not associated with significant haemodynamic disorders. The incidence of haemodynamic valve disorders in APS is approximately 1 to 4 % [22]. Valve involvement can manifest through global valve thickening, local thickening, usually involving the proximal or middle part of the leaflet, uneven nodes or verrucous vegetations on leaflets (known as Libman-Sacks endocarditis (LSE); mild to moderate valve dysfunction [9, 15, 17, 20, 24, 25].

A prospective study by N. Nagy et al. [26] compared the incidence of CVD variants in patients with SLE with aPLA (n = 258, 69.9 %) and without aPLA the (n = 111, 30.1 %). All cardiac manifestations were more common in the aPLA group; however, a significant difference was found in tricuspid (31.4 % vs. 18.0 %, p = 0.008) and mitral insufficiency (33.7 % vs. 21.6 %, p = 0.02). Besides, patients with aPLA have statistically significantly more such clinical manifestations of SLE, as disorders of the CNS (n = 73, 28.3 % vs n = 14, 12.6 %, p=0.001), peripheral nervous system (n = 32, 12.4 % vs n = 6, 5.4 %, p = 0.043) and mental disorders (n = 60, 23.3 % vs n = 14, 12.6 %, p = 0.019), which can be partially attributable to CVD and its complications.

Table 1. *Classification criteria for antiphospholipid syndrome (ACR/EULAR, 2023)*

Clinical criteria	Weight, scores
Domain 1 — Macrovascular (venous thromboembolism, VTE)	
• VTE with a high-risk VTE profile	**1**
• VTE without a high-risk VTE profile	**3**
Domain 2 — Macrovascular (arterial thrombosis, AT)	
• AT with a high-risk CVD profile	**2**
• AT without a high-risk CVD profile	**4**
Domain 3 — Microvascular	
Suspected (one or more of the following):	
• livedo racemosa (by physical examination)	**2**
• livedoid vasculopathy lesions (by physical examination)	
• Acute/chronic aPl nephropathy (by physical examination or laboratory tests)	
• Pulmonary hemorrhage (by clinical symptoms and imaging)	
Established (one or more of the following):	
• livedoid vasculopathy (by pathology)	**5**
• Acute/chronic aPl nephropathy (by pathology)	
• Pulmonary hemorrhage (by BAL or pathology)	
• Myocardial disease (by imaging or pathology)	
• Adrenal hemorrhage or microthrombosis (by imaging or pathology)	
Domain 4 — Obstetric	
• ≥3 consecutive pregnancy loss before 10 weeks and/or early fetal loss (10 weeks 0 days and 15 weeks 6 days)	**1**
• Fetal death (16 weeks 0 days — 34 weeks 0 days) without preeclampsia with severe features or placental insufficiency with severe features	**1**
• Preeclampsia with severe features (<34 weeks 0 days) **or** placental insufficiency with severe features (<34 weeks 0 days) with/without fetal death	**3**
• Preeclampsia with severe features (<34 weeks 0 days) **and** placental insufficiency with severe features (<34 weeks 0 days) with/without fetal death	**4**
Domain 5 — Cardiac valve	
• Valve thickening	**2**
• Valve vegetation	**4**
Domain 6 — haematology	
• Thrombocytopenia (20-130×10^9/liter)	**2**
Laboratory Criteria	
Domain 7 — aPl test by coagulation-based functional assay	
• Positive LAT (single-one time)	**1**
• Positive LAT (persistent)	**5**
Domain 8 — aPL testing by solid-phase assays: aCL and/or anti-β2GPI antibody enzyme-linked immunosorbent assay	
• Moderate or high positive (IgM alone) (aCL and/or anti-β_2GPI)	**1**
• Moderate positive (IgG) (aCL and/or anti- ß$_2$GPI)	**4**
• High positive (IgG) (aCL **or** anti-β_2GPI)	**5**
• High positive (IgG) (aCL **and** anti-β_2GPI)	**7**

Note. APS is classified for research purposes if there are at least 3 points from clinical domains **and** at least 3 points from laboratory domains
Abbreviations: AT — arterial thrombosis, VTE — venous thromboembolism, aPL — Antiphospholipid antibody, BAL — bronchoalveolar lavage, BP — blood pressure, CVD — cardiovascular disease, LAT — lupus anticoagulant, aCL — anticardiolipin antibody, anti-β_2GPI — anti-β_2-glycoprotein I antibody. Adapted from M. Barbhaiya et al. [2].

Table 2. *Comparison of formulations of valvular heart disease in APS based on the materials of the APS Congresses 2006 and 2023*

The 2006 APS classification criteria **Definition of aPL-associated valvular heart disease**	**The 2023 APS classification criteria** **Domain 5 — Cardiac valve**
Coexistence of aPL (Laboratory Criteria for APS) along with: - Echocardiographic detection of lesions and/or Regurgitation and/or stenosis of mitral and/or aortic valve or any combination of the above. - Defining valve lesions include: - Valve thickness >3 mm, - Localized thickening involving the leaflet's proximal or middle portion, - Irregular nodules on the atrial face of the edge of the mitral valve, and/or the vascular face of the aortic valve.	Criteria for inclusion and: - Valve thickening - MV thickening is defined as >4 mm between ages 20–39 years; >5 mm for those older than age 40 years, and>3 mm for other valves for any age (valve thickening can be associated with valvular dysfunction (regurgitation or stenosis)). - Valve vegetation is defined as shaggy, lobulated, or rounded masses typically located on the atrial side of atrioventricular valves (MV and tricuspid valve) or ventricular side of the AV, but can be located on any side of any valve (size is highly variable but usually <1 cm).

Notes: APS — antiphospholipid syndrome; AV — aortic valve; MV — mitral valve; aPL — antiphospholipid antibodies. Adapted from S. Miyakis et al. [14] и M. Barbhaiya et al. [2]

A large systemic review and meta-analysis conducted by S. Zuily et al. [27] reported that aPLA in patients with SLE is associated with 3-fold increase in the risk of CVD, including LSE. The available data are the most conclusive evidence of the correlation between aPLA and damages to the heart valves.

A meta-analysis of 25 studies with the total number of 8,089 patients with SLE showed that the presence of aPLA significantly increased the risk of CVD (HR = 2.24, 95 % CI: 1.58–3.18, p < 0.001) [22]. It is worth mentioning that among the laboratory findings, the highest risk of CVD is typical for LAC (HR = 4.90, 95 % CI: 2.26-10.60, p < 0.001). Positive aCA test doubled the risk (HR = 2.69, 95 % CI: 1.47–4.93, p = 0.001), while positive anti-β_2GP1 test increased the risk by 70 % (HR = 1.70, 95 % CI: 1.17–2.45, p = 0.005).

Pathogenesis

The pathogenetic mechanisms of CVD in APS have not been studied sufficiently; however, aPLA is assumed to have the leading role in endocardium damage [9, 17, 28, 29]. Both inflammatory and thrombolytic mechanisms associated with aPLA have been discussed [25, 30]. In APS patients, endothelial damage results from the action of autoantibodies targeting negatively charged phospholipids in endothelial membranes, endothelial microdamages caused by shear stress or blood flow turbulence, as well as antibody production due to molecular mimicry associated with infectious agents [9, 19, 25, 31]. Valve endothelium damage leads to local platelet aggregation, inflammatory mononuclear cell migration and deposits of immune complexes forming a blood clot intertangled with fibrin [32]. A number of studies demonstrated positive correlation between aCA titer and CVD severity [15-17, 25, 33, 34]. Initial inflammatory changes cause subsequent subendocardial inflammation, vascular proliferation, fibrosis, calcification, leading to leaflet thickening, rigidity and in some cases commissure fusion [35, 36].

L. Ziporen et al. [36] found aPLA deposits and complement components in tissues of deformed cardiac valves in patients with primary SLE-associated APS. The data confirm the pathogenetic value of aPLA in the development of valve damage in APS. Moreover, affected valves of patients with APS showed anti-b_2GP1 antibodies, among which at least anti-b_2GP1-associated peptides were target epitopes of these antibodies [37]. The peptides had a similar amino acid sequence with various bacterial and viral antibodies. Based on the data, the authors assumed that non-bacterial LSE can be indirectly caused by an infection due to molecular mimicry and production of antibodies initially targeting infectious agents.

It is assumed that aPLA and especially LAC associated with pronounced hypercoagulation [38] are critical for the pathogenesis of heart valve destruction in SLE patients [25, 30]. LSE is secondary to deposits of fibrinous platelet plugs on the affected valve. It is likely that aPLA facilitate blood clotting on valves, which are already damaged by inflammation [17, 25].

A study by Yu. S. Bakhareva et al. of the role of polymorphism of 18 candidate genes in the development of non-infectious endocarditis in patients with APS showed that polymorphism of some genes is reliably associated with valve damages, suggesting genetic susceptibility in these patients [20].

Morbid anatomy

The histologic pattern of aPLA-associated valvulopathy is non-specific and includes fibrosis, calcification, vascular proliferation, verrucous deposits on the valve endocardium, and thrombotic capillaries in the valve. Typical verrucous vegetations are represented by low, flat warted formations with a fibrous plaque and focal calcification. Vegetation formation is associated with marked scarring, fibrous tissue proliferation, often resulting in leaflet thickening and valve deformity with later valve dysfunction [9, 31]. Usually vegetations in APS patients are small (up to 10 mm), but sometimes they can be large (≥ 10 mm) and are located in any place on the endocardial surface, in some cases resulting in valve insufficiency. Vegetations typical for LSE in SLE patients are reported approximately in 10 % of patients and correlate with the disease duration and severity as well as aCA [9, 24].

Clinical presentation

APS patients are often asymptomatic or have unclear clinical manifestations, which make timely diagnosis of the syndrome and CHD challenging. Clinical manifestations and instrumental findings can resemble presentations of infectious endocarditis (IE) or rheumatic heart disease. It is not uncommon that LSE vegetations mimic cardiac myxomas [35, 40]. In valve insufficiency or stenosis, clinical manifestations are influenced by the respective valve pathology. The majority of patients remain asymptomatic for a long period of time and just some of them develop cardiac failure and need heart surgery [31, 41]. Absence or unclear symptoms of CVD are the cause of unawareness on the part of clinicians as to the possible endocardium involvement in APS patients [15].

CVD in APS patients requires special attention not only because of valve dysfunction development, but also due to the risk of arterial thromboembolic complications (TEC), including strokes [20, 25, 42]. Unlike IE, LSE vegetations are sterile, more loose and prone to embolization [19, 43]. In case of APS with MV involvement, the rate of arterial embolization is as high as 77 % [23].

A prospective study by J. Pardos-Géa et al. demonstrated that CVD in patients with APS is associated with 8.4-fild risk of arterial thrombosis within the 12-month period [44]. Similar results were obtained in a prospective study by S. Morelli et al. [45], who noted that left-sided CVD is a powerful risk factor of cerebrovascular conditions in patients with SLE. The authors found out that the presence of CVD is associated with a 10.8-fold increase in the risk of stroke and/or transient ischemic attack.

In 2005, S.A. Roldan et al. [46] suggested that CVD in patients with SLE causes ischemic brain damage and cardiovascular pathology. An examination of 37 patients with SLE showed that LAC, moderately thickened MV leaflets or mitral valve insufficiency were associated with a 10-fold increase in the risk of cerebral infarction. Besides, in patients with SLE, CVD diagnosed with the help of transthoracic echoCG (TTE) is an independent predictor of a brain damage shown on magnetic resonance imaging (cerebral infarction, white matter damages or small pinpoint abnormalities), neurological disorders (strokes, transient ischemic attacks, cognitive dysfunction) and mental disorders (acute confusional state consciousness, fits or psychosis) [47].

In a large study of 284 patients with APS, I. Krause et al. [48] established that CVD is associated with higher rates of impaired cerebral circulation, epilepsy and migraines. A sub-analysis showed significant correlation between CVD (vegetations and/or thickened valve leaflets) and CNS abnormalities in patients with primary APS; however, there was no such correlation in patients with secondary SLE-associated APS.

R. Cevera et al. [49] demonstrated that, in patients with APS, the rate of TECs during the first five years and subsequent five years of follow-up was 16.6 % and 14.4 %, respectively. According to a number of studies, the most common TEC in APS is strokes (19.8–35.2 %), myocardial infarction (7.4–8.64 %), transient ischemic attacks (4.7 %), deep venous thrombosis (4.3 %) and pulmonary artery thromboembolia (3.5 %) [20, 48, 49].

The data of a prospective 12-year follow-up of 53 patients with APS demonstrate that CVD is often associated with TEC [44]. For instance, patients with baseline echoCG signs of valvulopathy vs. controls without signs of CVD more often had arterial thrombosis (69 % vs. 20 %, $p < 0.001$), risk factors of atherosclerosis (62 % vs. 29 %, $p = 0.01$), *livedo reticularis* (48 % vs. 16 %, $p = 0.01$), and migrain (41 % vs. 12 %, $p = 0.02$). CVD (thickened leaflets and verrucous vegetations) can be a risk factor of CNS damage, early onset of atherosclerosis and severe underlying disease [44].

Results of a recent study by S. Niznik et al. [42] to analyse the clinical characteristics and outcomes of primary APS with CVD show that patients with APS and CVD more often have cerebrovascular events (56.3 % vs 25 %, $p = 0.005$) and *livedo reticularis* (24.2 % vs. 7.8 %, $p = 0.013$), as compared to patients with intact valves. Besides, unlike patients with APS without valve pathologies, patients with APS and CVD more often had catastrophic APS (12.1 % vs. 2.4 %, $p = 0.034$), recurrent

thrombosis (33.3 % vs. 4.7 %, p < 0.001) and needed effective therapy (IV immunoglobulin, plasma exchange or rituximab). Given the more severe course of APS in patients with CVD, the authors think that the valve pathology is a high risk APS category [42].

Diagnosis of cardiac valve disease in patients with antiphospholipid syndrome is based mostly on the TTE results, the sensitivity and specificity of which are 35–45 % and 75 %, respectively. The most common echoCG sign is locally thickened proximal and middle part of leaflets, diffuse increase in leaflet thickness (> 3 mm), uneven nodes on any side of any valve (usually MV and/or AV), endocardium vegetation [9]. Not uncommon are the so-called kissing foci, located on the opposite sides of the closing line on both MV and AV [25, 50].

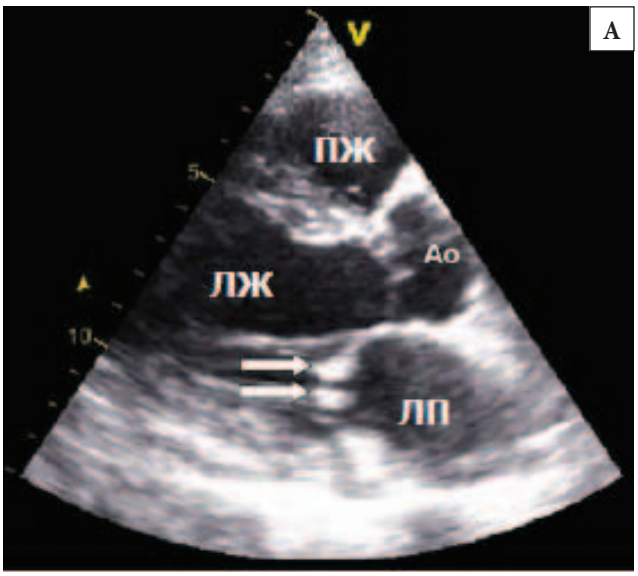
According to prospective echoCG studies, CVD in APS patients persists or progresses, irrespective of the use of anticoagulants or antiplatelet therapy [24, 50].

TTE should be considered as primary screening of CVD in APS patients; it should be used to monitor the efficiency of anticoagulant therapy (ACT), which in some cases allows minimising or removing vegetations [9].

When transesophageal echoCG (TEE) is used, sensitivity is higher (73–97 %); however, its specificity drops (37 %). The use of TEE is justified to explore the characteristics of CVD and to find any changes, which cannot be identified with TTE [18, 41, 51, 52]. Better findings of verrucous endocarditis visualisation in TEE result from the use of high-frequency sensors, which ensure better quality of images and make it possible to see even tiniest changes. According to the results of a meta-analysis of 11 studies, the rate of CVD in patients with SLE, as shown by TTE, and aPLA is statistically higher than in patients with negative aPLA: 131/300 (44 %) vs. 120/488 (25 %), p < 0.0005 [41]. At the same time, there is a comparable rate of CVD signs seen at TEE in patients with SLE with and without aPLA: 30/50 (60 %) vs. 26/41 (63 %), p = 0.9. Thus, TEE demonstrates higher sensitivity in identification of valve pathologies in patients with SLE depending on aPLA status: 44 % seen at TTE vs. 60 % seen at TEE in patients with SLE and aPLA (p < 0.04) and 25 % seen at TTE vs. 63 % seen at TEE in patients with SLE without aPLA (p < 0.0005).

When TTE is used, valve pathologies in patients with APS are diagnosed more often than in healthy population: 55 out of 137 (40 %) and three out of 125 (2 %), p < 0.0001, respectively. Patients with primary APS have more cases of CVD when TEE is used as compared to TTE: 132 out of 180 (73 %) and 61 out of 157 (39 %), p < 0.0005, respectively [41].

Diagnosis of non-bacterial thrombotic endocarditis (NBTE), which includes LSE, can be more challenging because of smaller size of vegetations after embolization,



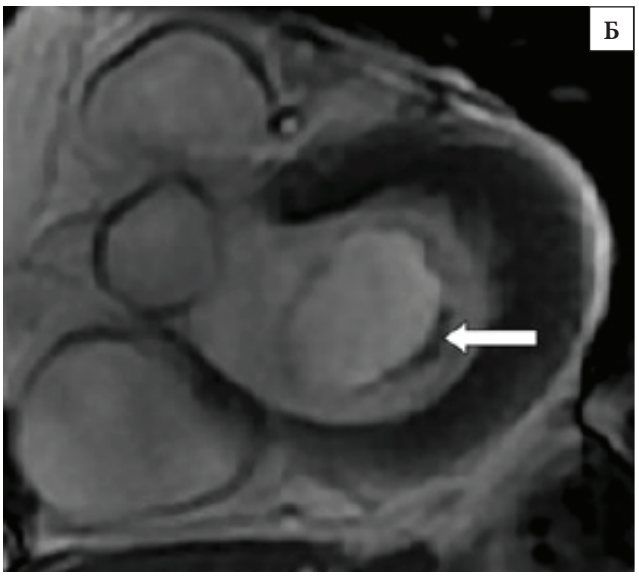


Figure. 1 *66-year-old male patient with APS:*
A. *Echocardiography, parasternal long axis view. The "kissing" vegetation is clearly visualized (marked with white arrows), located near the free margins of both mitral leaflets come into contact during systole.*
B. *Cardiac magnetic resonance imaging parasternal short axis view. The arrow indicates a localized thickening (dark color) of the distal part of the MV leaf. Adapted from S. Zuily et al. [25].*
Notes: RV — right ventricle; LV — left ventricle; LA — left atrium; Ao — Aorta

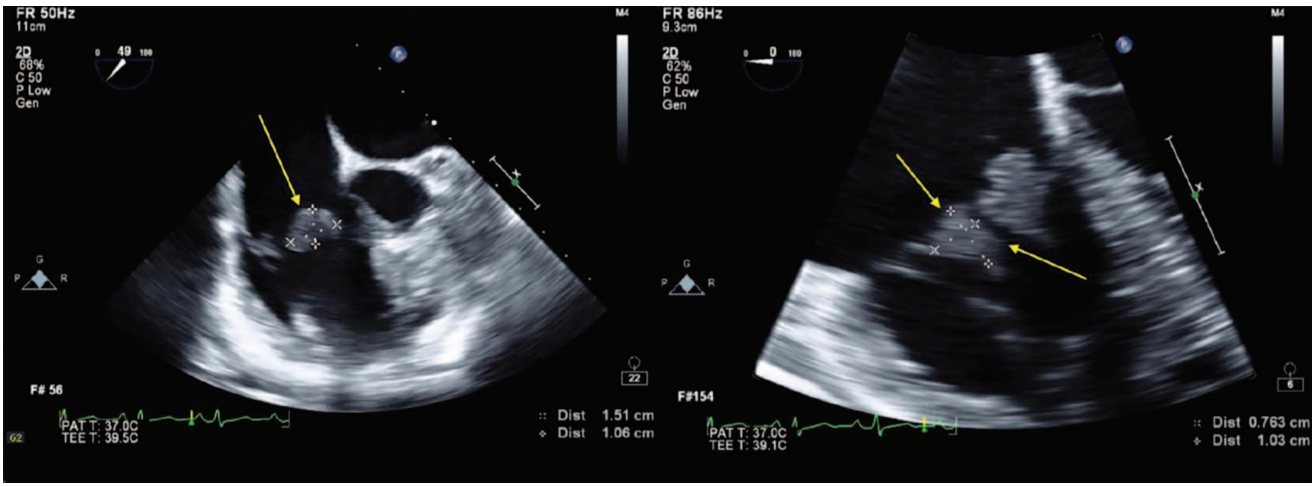


Figure 2. *A 44-year-old female patient, secondary antiphospholipid syndrome associated with systemic lupus erythematosus. Transesophageal echocardiogram. On the left: non-bacterial vegetation (marked with an arrow) on the anterior leaflet of the tricuspid valve measuring 1.51×1.06 cm. On the right: vegetation is also visualized on the posterior leaflet of the tricuspid valve measuring 0.76×1.03 cm. Adapted from T. Nagi et al. [43]*

which a common cause of false negative results of initial echoCG. M. A. Zmaili et al. [18] followed up a 47-year-old patient with SLE and significant mitral insufficiency, as shown by TTE and TEE, and with no evident signs of endocarditis. However, a histopathological examination after MV prosthesis revealed NBTE. Thus, diagnosis of CVD in patients with APS requires high clinical suspicion [18, 53].

There are publications on the use of 3D real-time TEE as an additional imaging method in patients with suspected CVD and APS [24, 25, 54]. As for other imaging methods, heart CT and MRI are alternative methods to diagnose cardiovascular conditions, including detection of endocavitary clots; they are also useful for differential diagnosis of the nature of endocardium involvement (Fig. 1–3) [24, 25, 40].

Management

Patients with APS are at a higher risk of primary and recurrent TEC, irrespective of their CVD status, that is why management of such patients requires discussion of preventive measures [55]. Given that estimated risks in studies vary a lot, several models for APS prediction were proposed in order to identify patients who will benefit from antithrombotic preventive measures [56, 57].

In 2003, the International Expert Committee published recommendations for the treatment of cardiac pathologies, including CVD, in patients with APS [58]. For instance, symptomatic patients with signs of valvulopathy are recommended ACT. Antiplatelet drugs can be used in asymptomatic patients for prevention.

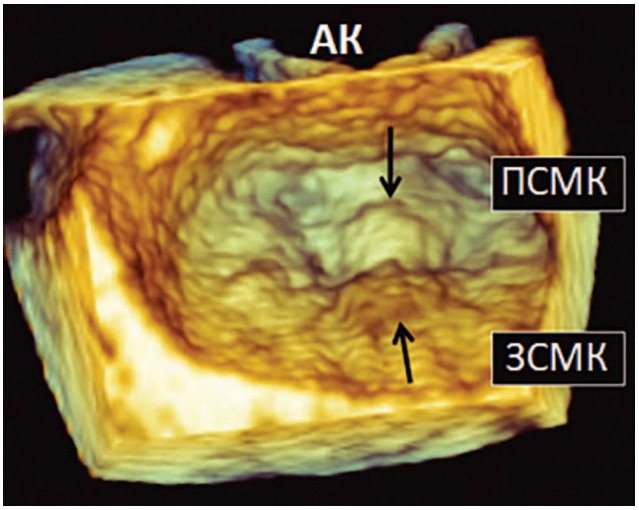


Figure 3. *Libman–Sacks endocarditis in the performance real time 3D transesophageal echocardiography. Face view of the mitral valve seen from the left atrial perspective. Mitral valve Libman–Sacks endocarditis appears as mound-like protuberances (arrows) on the tips of the A2 scallop of the anterior leaflet and the P2 scallop of the posterior leaflet. AV — aortic valve; AML — anterior mitral leaflet; PML — posterior mitral leaflet*

For patients with APS and CVD, immunosupressive, antiplatelet, anticoagulant therapy and surgical correction of valve defects are indicated [17, 40, 43, 51, 59].

The results on the efficacy of ACT to reduce the size of vegetations and the risk of TEC, are controversial [15, 18, 60]. According to the data on case studies and series of cases, the use of anticoagulants, hydroxychloroquine (HCQ) and glucocorticoids (GC) can reduce the size of

vegetations or eliminate them within a period from one week to one year, including regression of relatively large masses (with the baseline size of 2 to 4 cm) (Table 3). At the same time, there are some reports on the absence of any effects of antiplatelet and anticoagulant therapy [40, 52, 79, 80]. It is worth mentioning that, in a number of LSE cases refractory to traditional therapy, vegetation was found on TV, despite the fact that the right-sided valves are rarely involved, as compared to MV and AV [40, 79, 80].

NBTE is also treated with immunosuppressants: HCQ and GC. By targeting platelets, endothelial and immune cells, HCQ reduces inflammation and the risk of blood clotting. A number of studies demonstrated favourable effects of HCQ in the reduction of the risk of blood clotting in patients with APS and asymptomatic aPLA carriers [72, 76, 81, 82]. A very low risk of haemorrhagic complications with the use of HCQ should be mentioned [81, 82].

It is assumed that GCs are justified in patients with CVD in secondary APS caused by an autoimmune condition, despite the current discussions of their benefits [73]. Some papers mention the ability of GC to significantly reduce the overall disease severity, leading to clinical improvements as regards valve structure and functions [83, 84]. Despite the mentioned favourable effects, it is still uncertain whether CGs should be prescribed, given their cardiovascular side effects (arterial hypertension, increased post- and preload, intensification of atherosclerosis processes, etc.). There is also little evidence in favour of GCs in CVD and primary APS [15, 73]. During the study of outcomes in patients who underwent heart valve surgery, T. Eviatar et al. [85] noted a higher rate of complications in the group of patients who were treated with CGs perioperatively vs. patients who did not take any steroids. It is assumed that GCs are prescribed to patients with a more severe course of disease, where visceral organs are involved, which also impacts the rate of complications of cardiovascular interventions. Besides, GCs predispose patients to infections and haemorrhagic complications [85].

Indications for cardiac surgery in patients with LSE remain unclear, while valve replacement results are limited to case studies or series of cases. According to Y. Le Ho et al. [31], the clear indications for surgery in patients with APS are severe valve dysfunction, large vegetations and recurrent embolism, despite ACT. Besides, unlike IE, NBTE is associated with a higher surgical risk of embolism with whole vegetations or their fragments due to higher susceptibility of APS patients to TEC [86]. As opposed to IE, where the valve needs to be dissected completely in order to remove infected tissue, in LSE patients, valve replacement and reconstruction can be sufficient, and there is no need for life-long ACT [31].

Patients with APS, who underwent heart surgery, demonstrate a higher risk of post-surgery complications and mortality caused by bleeding or blood clots [15, 51, 85, 87]. In addition to bleeding and blood clots, common post-surgery complications include sepsis, heparin-induced thrombocytopenia, as well and rhythm disturbance and impaired conductivity [88, 89]. According to T. Eviatar et al. [85], out of 26 patients, who underwent surgery for CVD in AOS, severe complications were reported in 14 patients (53.8 %), including four deaths (15.4 %). N. B. Chalvon et al. [89] followed up 23 patients with SLE and/or APS, who underwent heart surgery. Nine (39 %) patients had early post-surgery complications, including three cases of dramatic APS and death.

S. Masoumi et al. [91] describes a 32-year-old female patient with primary APS, who was diagnoses with MV LSE in addition to significant mitral insufficient (TEE procedure). Two vegetations were found: one 30×5 mm, attached to the base of the anteromedial side of MV leaflet; and a larger one measuring 26×12 mm at the anterior MV leaflet. The patient underwent heart surgery to dissect vegetations and partially reconstruct the MV using autologous pericardium and a pair of artificial chords. Four months later, the patient developed signs of pulmonary hypertension and right ventricular failure. TEE showed severe TV and MV failure, as well as perforated pericardial flap on the reconstructed MV, requiring another heart surgery to impact an artificial MV and repair TV.

In a retrospective analysis of 32 patients with APS, who underwent valve replacement, early mortality was 7 %, long-term mortality — 12.5 % [92]. Only 42 % of patients who underwent heart valve surgery recovered without complications. Higher mortality rates (up to 20 %) were recorded in other studies [87, 93]. Assessment of thrombotic and haemorrhagic risks, as well as close monitoring of the patient's condition and valve function evaluation in the post-surgery period are essential for reduction of the rate of complications [51, 85, 87]. Since there are no results of long-term follow-ups, the opinion on prosthetic valve selection remains unclear: whether it should be mechanic or biological one. In patients with primary or secondary APS, antibacterial therapy to prevent IE is considered unjustified [15, 88].

Table 3. *Results of drug therapy in the treatment of vegetations in antiphospholipid syndrome*

№	First author	Year	Age, gender	Presentation	Autoimmune disease	Affected valve	Vegetation size (cm)	Treatment	Time to dissolution
1.	Skyrme-Jones R [61]	1995	16, F	Strokes	PAPS	MV	0,8×0,5	VKA	9 months
2.	O'Neill D. [62]	1995	40, F	Strokes	PAPS	MV	NA	VKA	7 weeks
3.	O'Neill D. [62]	1995	47, F	Splinter hemorrhages	PAPS	MV	NA	heparin, VKA	6 weeks
4.	Agirbasli M.A. [63]	1997	56, F	STEMI	PAPS	MV	0,3 и 0,8	VKA	4 months
5.	Ebato M. [64]	2002	62, F	PE	PAPS	TV	1,7×1,8	heparin, VKA	7 days
6.	Tomcsanyi J. [65]	2004	58, F	Splenic infarct	PAPS	MV, TV	NA	Anticoagulants	6 weeks
7.	Brito F.A. [66]	2004	34, F	Murmur	SLE, APS	MV	NA	VKA	6 months
8.	Ruan Y. [67]	2008	43, F	TIA	Seroneg. APS	MV	1,0	Aspirin, heparin, warfarin	42 days
9.	Salzberg S.P. [68]	2009	30, м 30, F	Strokes	PAPS	AV	4×2,0	heparin	4 months
10	Prashanth P. [69]	2011	27, F	Incidental TTE	Seroneg. RA, SLE, APS	MV, PAV	2,0	heparin, with subsequent reception VKA (INR 2-3)	4 weeks
11	Stevanovic D. [70]	2014	33, F	Erythematous rash	PAPS	MV	NA	LMWH, CS, cytostatics	1 year
12	Rachwan R.J. [71]	2017	38, F	TIA, murmur	PAPS	AV	3,7×2,1	LMWH	4 months
13	Yuriditsky E. [59]	2018	36, м F	Strokes	PAPS	AV	2,7	LMWH	21 days
14	Yuriditsky E. [59]	2018	29, м 29, F	Strokes	SLE, APS	AV	2,8	Heparin	9 days
15	Sirinvara-vong N. [72]	2018	65, F	Incidental TTE	PAPS	MV	1,4×0,7	LMWH, HCQ, CS	6 months
16	Granowicz E. [73]	2018	43, F	Chest pain, dyspnoea	SLE, APS	AV	2,0	1. Rivaroxaban 2. HCQ, CS	1. 0 effect 2. 24 weeks
17	Kitano T. [74]	2019	51, F	Dizziness, right-sided ataxia	SLE, APS	AV	NA	1. Apixaban 2. Heparin	1. 0 effect 2. 7 days
18	Shipman J. [75]	2020	64, F	Incidental TTE	PAPS	Mitral	1) 1,4×0,9 2) 1,3×0,8	VKA	8 weeks 1. full resolution 2. reduced to 1,2×0,3
19	Haertel F. [76]	2021	27, F	Night sweats, weight loss, reduction in performance, dizziness	PAPS	MV	1,6×0,9	VKA (INR 2-3), HCQ, CS	3 months
20	Bahar AR. [77]	2024	47, F	Chronic weakness, weight loss	PAPS	AV	0,61×1,2	VKA, rivaroxaban, dabigatran	2 months
21	Bowden A [78]	2024	60, F	Strokes	SLE, APS	MV	0,4 × 0,4	LMWH, VKA	25 days

Abbreviations: TIA — transient ischemic attack, TTE — transthoracic echocardiogram, PE — pulmonary embolism, APS — antiphospholipid syndrome, PAPS — primary APS, Seroneg. — seronegative, SLE — systemic lupus erythematosus, RA — rheumatoid arthritis, AV — aortic valve, MV — mitral valve, PAV — pulmonary artery valve, TV — tricuspid valve, NA — not available, INR — international normalized ratio, VKA — vitamin K antagonist, LMWH — Low-molecular-weight heparin, CS — corticosteroids, HCQ — hydroxychloroquine, 0 effect — no effect.

Conclusion

CVDs are the most common cardiac pathology in patients with APS, which is diagnosed approximately in one third of patients; it is associated with local, diffuse thickening of leaflets, development of verrucous endocarditis, valve failure and (in rare cases) stenosis. Diagnosis of CVD is based mostly on echoCG findings, including TEE. CVD is often associated with various TECs, such as cerebrovascular disorders, arterial or venous thrombosis, myocardial infarction, migraines, and mental disorders. Management of patients with CVD and APS is challenging, given the lack of any conclusive evidence in favour of the use of immunosuppressive, antiplatelet and anticoagulation therapy. In case of significant valve dysfunction, patients with APS should be consulted by a heart surgeon in order to decide whether surgery is required or not, because the risk of post-surgery complications is high.

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Contribution of authors:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Ignatenko G.A. — idea of the article, organization and integration of the authors' team, final editing and approval of the manuscript

Taradin G.G. — collection, analysis and interpretation of data, formulation of conclusions, editing of the manuscript; author's agreement to be responsible for all aspects of the work

Kononenko L.V. — collection, processing of material, literature review

Rakitskaya I.V. — writing and editing the manuscript

Kagitina Y.S. — collection of material, literature review, preparation and design of work

Prendergast B.D. — writing individual sections of the manuscript

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