Srce i krvni sudovi 2025; 44(2) : 25-30

Case report

Presence of endothelial dysfunction expressed by flow-mediated brachial artery dilation values in patients with primary antiphospholipid syndrome

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Abstract

Introduction: *Primary antiphospholipid syndrome (PAPS) is a rare autoimmune disease characterized by arterial/venous thrombosis and/or obstetric pathology in the presence of antiphospholipid antibodies (aPL). Evidence suggests that aPL directly interact with membrane phospholipids of endothelial cells, leading to endothelial dysfunction (ED) and accelerating atherosclerosis.*

Methods: *This study aimed to establish the presence of ED, expressed by a decrease in the percentage of flow-mediated brachial artery dilation (FMD), in a cohort of 100 Serbian PAPS patients without previously diagnosed cardiovascular disease. All participants underwent clinical evaluation to identify standard atherosclerotic risk factors. Tested aPL included: lupus anticoagulant (LA), anticardiolipin antibodies (aCL IgG/IgM), and anti-ß2-glycoprotein I antibodies (a-ß2GPI IgG/IgM). FMD was measured following standardized patient preparation and compared to results from 80 healthy controls.*

Results: *The study cohort consisted predominantly of females age 47.7 ± 8.5 years with a low prevalence of conventional risk factors. ED, reflected by reduced FMD values, was present in 37.6% of PAPS patients, significantly more than in the control group (p = 0.0001). Age (p = 0.041) and glycemia value (p = 0.045) were significantly associated with ED. However, aPL type and clinical manifestations were not. Multivariate regression including age, glycemia value and thrombosis history showed no independent predictors of ED.*

Conclusion*: ED is significantly more prevalent in PAPS patients than in healthy individuals, and represents a direct consequence of the autoimmune process. Earlier involvement of a cardiologist and appropriate management may reduce the risk of future cardiovascular complications.*

Keywords *primary antiphospholipid syndrome; endothelial dysfunction; cardiovascular risk*

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder that is clinically characterized by recurrent thromboses (arterial and/or venous) and/or recurrent spontaneous abortions and, in the laboratory, by the persistent presence of antiphospholipid antibodies. The disease can occur in isolation (primary APS (PAPS)) or in association with other conditions, most commonly systemic lupus erythematosus[1]. It was first described in 1983 and is also referred to in the literature as Hughes syndrome[2]. According to epidemiological studies, the prevalence of APS is estimated to be around 50 cases per 100.000 inhabitants. Thus, this disease is considered rare[3]. The disease predominantly occurs in women with a low prevalence of standard atherosclerotic risk factors[4].

Antiphospholipid antibodies (aPL) encompass a wide range of antibodies directed against the phospholipids of the cell membrane. Today, the diagnostic criterion for antiphospholipid syndrome is the presence of lupus anticoagulant (LA), anticardiolipin antibodies (aCL) of IgG and IgM classes, and anti-β2-glycoprotein-I antibodies (aβ2GP-I) of IgG and IgM classes, detected at least twice within a 12-week interval[5].

The pathophysiological mechanism of thrombophilia in APS is explained by the binding of aPL to the membrane of endothelial cells, which thereby become dysfunctional. The secretion of cytokines and the expression of adhesive molecules increase, making the endothelium prothrombotic[6]. On the other hand, endothelial dysfunction (ED) is the initial event in the process of atherogenesis, so this mechanism explains the increased risk of non-thrombotic cardiovascular manifestations and ac-

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celerated (premature) atherosclerosis in these patients[7,8].
Cardiovascular manifestations of APS are consequently very diverse and can be the result of thrombosis that can occur in any blood vessel[9]. Among the non-thrombotic manifestations of APS, the most frequently observed changes are in the valves, characterized by thickening of the cusps and their dysfunction, and non-infectious valve thrombosis (Libman-Sacks endocarditis), along with the development of coronary disease and premature myocardial infarction[10]. In less than 1% of patients with APS, catastrophic APS (CAPS) can develop, characterized by multiple thromboses in various organs and multiorgan dysfunction, with a mortality rate of around 50%[11].
A simple and non-invasive method for determining the presence of ED is the measurement of flow-mediated dilation (FMD) of the brachial artery, which was established by Celermajer back in 1992[12]. The safety of this method in assessing endothelial function has been confirmed through the results of numerous studies[13,14].
This study aims to investigate the presence of endothelial dysfunction by measuring flow-mediated dilation in patients with PAPS, without a prior diagnosis of cardiovascular disease.

Methods

Study population

This is a cross-sectional observational study of a Serbian cohort of 100 patients with PAPS. The diagnosis of APS was made by rheumatologists according to the revised Sydney criteria (laboratory and clinical) from 2006. Clinical criteria include the detection of vascular thrombosis (one or more episodes of thrombosis in arteries, veins, or small blood vessels in any tissue or organ) and/or complications in pregnancy (one or more unexplained deaths or morphological abnormalities of the fetus at or after 10 weeks of gestation, and one or more preterm births of a normal newborn before or at 34 weeks of gestation due to preeclampsia, eclampsia, or fetal growth restriction, and three or more unexplained spontaneous miscarriages before 10 weeks of gestation). Laboratory criteria include the presence of aCL-IgG/IgM at a moderate or high titer (dependent on β2-GPI) and LA, along with the necessity of a repeated positive finding of aPL within at least 12 weeks. The diagnosis of APS is established if at least one clinical and one laboratory criterion is present[15].
The primary exclusion criterion in our study was the presence of a previous cardiovascular disease (ischemic heart disease, heart failure).

Clinical examination

All patients underwent a clinical examination during which the presence of standard atherosclerotic risk factors was determined: heredity, hypertension, obesity, diabetes mellitus, hyperlipidemia, and smoking. Hereditary factors in cardiovascular diseases were defined as the occurrence of myocardial infarction, stroke, peripheral vascular disease, or sudden cardiac death in a family member before the age of 65 for men or before the age of 55 for women. We characterized hypertension if blood pressure was recorded above 140/90 mmHg on two or more consecutive examinations in patients who were not on antihypertensive therapy. The assessment of obesity was conducted based on the body mass index (BMI) according to the formula by Adolphe Quetelet (height/weight^2), where if the BMI exceeded 30 kg/m^2, the participants were classified as obese. Diabetes mellitus was diagnosed by endocrinologists[16]. Hyperlipidemia was present if cholesterol levels were above 5.2 mmol/l in two consecutive measurements, or if the patient was already undergoing therapy to lower cholesterol.

Laboratory tests

All patients were evaluated for the presence of antiphospholipid antibodies, accompanied by routine biochemistry and complete blood cell counts. Lupus anticoagulant (LA) was based on the initial use of phospholipid-depleted or platelet-depleted coagulation tests, such as kaolin clotting time (KCT), dilute Russell's venom viper time (DRVVT), the tissue thromboplastin inhibition test, and diluted activated partial thromboplastin time. The LA tests were not performed while the patients were receiving anticoagulant therapy. Anti-cardiolipin (aCL: IgG/IgM) and anti-ß2glycoprotein I (ß2GPI: IgG/IgM) antibodies were measured by an enzyme-linked immunosorbent assay (ELISA, Binding Site) and expressed in GPL or phospholipids (MPL) units (GPL-U and MPL-U).

Assessment of ED

The existence of ED was assessed by measuring FMD. The diameter of the brachial artery was measured using a high-resolution linear vascular ultrasound probe. Before the measurements, participants were instructed to refrain from taking vitamin supplements (at least 72 hours prior to measurement), caffeine (12 hours prior to measurement), and smoking cigarettes (at least 12 hours prior to measurement). For women in the reproductive period, measurements were conducted during the same phase of the menstrual cycle, at least 6 hours before eating, at least 12 hours after physical activity, before the intake of vasoactive medications, at least 3 days after taking aspirin, and 1 day after taking nonsteroidal anti-inflammatory drugs. Measurements were conducted in a quiet environment, at room temperature between 20°C and 25°C. Flow-induced dilation of the brachial artery was measured after the release of the blood pressure cuff, which had previously been inflated to 50 mmHg above the systolic blood pressure for a duration of 5 minutes to occlude flow through the artery. After the cuff was released, the diameter of the brachial artery was measured for 3 minutes. The difference in the values of the diameter of the brachial artery represented the percentage of FMD. The value of 7.1% was taken as the threshold for the normal degree of endothelial-dependent dilation of the brachial artery[17].
The obtained values were used as a marker for ED and were compared with the values obtained in the control group of 80 healthy participants, matched with the PAPS group according to sex, age, and the presence of stan-

Table 1: Clinical characteristics of the studied patient groups

Variables	PAPS (n=100)	Controls (n=80)	P value
Age (years)	47.7±8.5	47.2±8.5	0.822
Gender (m/f)	(16/84)	(12/68)	0.240
BMI (kg/m2)	26.7±3.3	25.6±4.6	0.149
Systolic BP mmHg	117.8±18.2	119.5±10.3	0.661
Diastolic BP mmHg	74.5±12.8	76.7±8.3	0.440
Pulse	75.3±12.5	76.3±6.2	0.717
Smoking	28 (28.0%)	21 (26.7%)	0.848
Hypercholesterolemia	35 (35.0%)	27 (34.3%)	0.935
Hereditary	27 (27.0%)	19 (23.4%)	0.626
Diabetes mellitus	9 (9.0%)	6 (8.5%)	0.756
Laboratory analysis:			
Leukocyte count 10^9	5.8±1.6	6.0±1.4	0.586
Platelet count 10^9	219.8±71.9	230.8±38.2	0.490
Hemoglobin (g/L)	134.7±13.0	135.3±14.5	0.836
Glycemia (mmol/l)	5.0±0.6	5.1±0.5	0.343
Total cholesterol (mmol/l)	5.3±1.1	5.5±0.9	0.690
LDL (mmol/l)	3.2±1.0	3.4±0.7	0.541
HDL (mmol/l)	1.5±0.4	1.5±0.4	0.848
Triglycerides	1.3±1.0	1.3±0.6	0.963
C-reactive protein	2.8±2.8	2.7±2.7	0.866

BMI – body mass index, BP – blood pressure, LDL – low-density lipoprotein cholesterol, HDL – high-density lipoprotein cholesterol

dard atherosclerotic risk factors.

The study meets the ethical guidelines of the latest Helsinki Declaration (Edinburgh, 2000) and has received approval from the Ethical Committee of the Faculty of Medicine at the University of Belgrade. All patients involved in the study have signed informed consent to participate in this research.

Statistical analysis

The statistical analysis of the obtained data was conducted using the statistical program SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) software package. In this study, descriptive and analytical statistical methods were used. Descriptive methods used included absolute and relative numbers (n, %), measures of central tendency (mean), and measures of dispersion (standard deviation). Among the analytical methods, difference tests were used: parametric (t-test) and non-parametric (Pearson's chi-square test, Fisher's exact probability test, Mann-Whitney U test). The choice of the test for testing the difference depended on the type of data and distribution. Parametric tests were used in the cases where the distribution was normal, and non-parametric tests were used if it was not. The normality of the distribution was examined based on descriptive parameters, tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests), and graphical methods (histogram, boxplot, QQ plot). For the analysis of relationships, logistic regression analysis was used, both univariate and multivariate. The results are presented in tabular and graphical form. All p-values less than 0.05 were considered statistically significant.

Table 2: Specific clinical and laboratory characteristics of the PAPS group

Characteristics	PAPS (n=100)
Specific clinical characteristics:	
Obstetric APS	67 (67.0%)
Thrombosis	58 (58.0%)
Arterial thrombosis	32 (32.0%)
Venous thrombosis	39 (39.0%)
CAPS	1 (1.0%)
ANA	18 (18.0%)
Anti-dsDNA	1 (1.0%)
aPL profile:	
LA	47 (47.0%)
aCL IgG	46 (46.0%)
aCL IgM	50 (50.0%)
anti β2 GPI IgG	41 (41.0%)
anti β2 GPI IgM	39 (39.0%)

CAPS – catastrophic antiphospholipid syndrome, ANA – antinuclear antibodies, Anti-dsDNA – anti-double-stranded DNA antibodies, aPL – antiphospholipid antibodies, LA – lupus anticoagulant, aCL – anticardiolipin antibodies, anti β2 GPI – anti-β2-glycoprotein-I antibodies

Table 3: FMD values in compared groups

Variables	PAPS (n=100)	Controls (n=80)	P value
FMD (%)	9.96±5.74	15.84±5.59	0.0001
Presence of endothelial dysfunction	38 (37.6%)	2 (2.5%)	0.0001

FMD – flow-mediated dilatation of brachial artery

Results

The clinical characteristics of the examined groups are presented in **Table 1**. PAPS patients are predominantly female (84%), with an average age of 47.7±8.5 years and a prevalence of standard atherosclerotic risk factors of less than 40%. The average values of blood pressure and BMI were within normal limits.

Table 2 presents the specific clinical characteristics of PAPS patients, and the aPL profile. In our cohort of PAPS patients, 67% were women with obstetric pathology, and 58% had thrombotic manifestations, with venous thrombosis (39%) being somewhat more common than arterial thrombosis (32%). When it comes to the types of aPL, the most prevalent was aCL IgM (50%).

PAPS patients had a significantly lower value of FMD in comparison to healthy participants (p=0.0001). ED was present in 37.6% of PAPS patients, and the difference was highly statistically significant compared to the control group (p=0.0001). The results are presented in **Table 3** and **Figure 1**.

In our study, statistical analysis revealed a significant correlation between age (p=0.041) and the glycemia levels (p=0.045), with the presence of endothelial dysfunction (ED), expressed through the percentage of FMD

Table 4: The impact of demographic characteristics and the presence of standard atherosclerotic risk factors on the presence of endothelial dysfunction in the PAFS group

Variables	Presence of endothelial dysfunction (n=38)	Absence of endothelial dysfunction (n=62)	P value
Age (years)	51.0±13.1	45.7±12.9	**0.041**
Gender (m/f)	6 (15.8%)/32 (84.2%)	10 (15.9%)/53 (84.1%)	1.000
BMI (kg/m2)	25.9±4.2	25.4±4.8	0.557
Hypertension	17 (44.7%)	17 (27.0%)	0.084
Smoking	9 (23.7%)	19 (39.2%)	0.647
Hereditary	12 (31.6%)	15 (23.8%)	0.487
Hypercholesterolemia	17 (44.7%)	18 (28.6%)	0.131
Diabetes mellitus	5.8±1.6	6.0±1.4	0.586
Glycemia (mmol/l)	5.2±0.6	5.0±0.5	**0.045**

Table 5: The relationship between the presence of ED and specific clinical and laboratory characteristics in PAPS

Variables	Presence of endothelial dysfunction (n=38)	Absence of endothelial dysfunction (n=62)	P value
Obstetric APS	9 (28.1%)	9 (17%)	0.277
Thrombosis	26 (68.4%)	31 (49.2%)	0.066
Venous thrombosis	18 (47.4%)	21 (33.3%)	0.206
Arterial thrombosis	16 (42.1%)	16 (25.4%)	0.121
Thrombocytopenia	4 (10.5%)	13 (20.6%)	0.273
LA	17 (44.7%)	30 (47.6%)	0.838
aCL IgG	21 (55.3%)	25 (39.7%)	0.152
aCL IgM	17 (44.7%)	33 (52.4%)	0.539
anti β2 GPI IgG	16 (42.1%)	25 (39.7%)	0.837
anti β2 GPI IgM	18 (47.4%)	21 (33.3%)	0.206

LA - lupus anticoagulant, aCL – anticardiolipin antibodies, anti β2 GPI - anti-ß2 glycoprotein-I antibodies

Tab**le 6:** Multivariate regression analysis of the predictors of ED development in PAPS

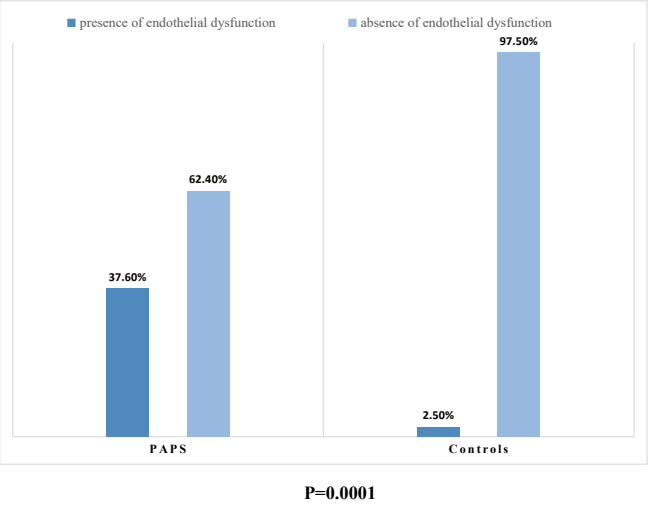
Variables	OR	CI (95%)	P value
Age	1.013	0.975-1.052	0.522
Thrombosis	0.594	0.226-3.721	0.291
Glycemia (mmol/l)	1.680	0.758-1.562	0.201

OR – odds ratio, CI (95%) - confidence interval

of the brachial artery. Correlation between ED presence and standard atherosclerotic risk factors are shown in **Table 4**.

The relationship between the presence of ED and specific clinical and laboratory characteristics in PAPS was also investigated. Patients with thrombotic APS had a somewhat higher degree of ED, but without a statistically significant correlation. No association was found between the aPL type and the presence of ED in PAPS

Figure 1: The presence of endothelial dysfunction in the examined groups of patients



patients. The results are presented in Table 5.

Through multivariate regression analysis that included age, glycemic values, and the presence of thrombosis in PAPS, no independent predictor of ED development in PAPS was identified (**Table 6**).

Discussion

Systemic autoimmune rheumatic diseases are associated with an increased cardiovascular risk, explained by systemic inflammation and the use of immunomodulatory therapy, which adversely affects the lipemic and glycemic profile and the blood pressure values[18]. APS, although initially thought of as a condition of acquired thrombophilia, has been linked in numerous studies to accelerated atherosclerosis and an increased risk of developing cardiovascular diseases[19]. The absence of systemic inflammation and, consequently, the application of immunomodulatory therapy, which would explain the adverse effect on the endothelium, make this autoimmune disease specific and allows for a clear connection between autoimmunity and endothelial dysfunction caused by the direct action of aPL[20].

In our cohort study, the presence of ED was examined in 100 PAPS patients by measuring the percentage of FMD. It was observed that the FMD values in PAPS were significantly lower (p=0.0001) and that ED was significantly more frequent in this group of patients compared to the healthy population. The presence of ED in APS has been confirmed by the results of numerous studies that identified specific markers, such as asymmetric dimethylarginine[21] and circulating endothelial cells, as markers of endothelial damage[22]. The focus of today's research is also the proinflammatory peptide amyloid-beta1-40 (Aβ40), which is considered to be a new marker of vascular inflammation, endothelial dysfunction, and atherothrombosis in the general population. In the study by Tektonidou and associates, this marker was significantly more present in the population of APS patients compared to healthy participants[23]. The study by Velasquez and associates showed the expression of various markers of endothelial dysfunction in different groups

of APS patients (thrombotic, obstetric, secondary, and therapy-refractory APS), highlighting their potential significance in understanding the appropriate treatment for these patients[24]. Our study showed that a simple, non-invasive method, such as measuring the percentage of FMD, can detect the presence of ED as a marker of early impact on the cardiovascular system and premature atherosclerotic process in PAPS.

Although the results of the small study by Bilor and associates highlighted that FMD value is significantly reduced in patients with aCL IgM antibodies, our study did not show a connection between aPL type and the development of ED[25]. It is evident that the type of aPL that leads to the development of ED is not crucial for its onset, but rather the mere existence of immune system activation and the presence of antibodies that interact with the membrane of endothelial cells.

Standard atherosclerotic risk factors lead to the development of atherosclerosis precisely through their negative impact on the endothelium. In our study, age and blood glucose levels were significantly associated with the presence of ED in PAPS, which was not confirmed for the other analyzed factors (smoking, diabetes, hypercholesterolemia and obesity). Such a finding can be explained by the low prevalence of these risk factors in the analyzed population. Misse and associates believe that traditional factors present in patients with APS act in synergy with non-traditional ones, significantly contributing to the worsening of ED[26]. Our study, among other things, shows that the development of ED in APS is not primarily a consequence of the negative effects of standard atherosclerotic risk factors, but rather of the immune response itself, i.e., aPL. Examining the impact of statins on aPL level in patients with systemic lupus erythematosus and coronary disease, it has been determined that this group of medications, in addition to their well-known anti-inflammatory effects, significantly reduces aPL level in patients with coronary disease, thereby also enhancing the influence of autoimmunity on the development of coronary atherosclerosis[27].

Study limitations

This study has certain limitations that should be acknowledged. First, it was conducted as a single-center cross-sectional observational study, which may limit the generalizability of the findings to other populations. Second, the relatively modest sample size might have reduced the statistical power to detect weaker associations, especially in subgroup analyses. Third, although FMD of the brachial artery is a validated and widely accepted method for the assessment of ED, it is operator-dependent and susceptible to variability despite standardized protocols. Additionally, some potential confounding factors, such as dietary habits, physical activity, and use of certain medications, were not systematically analyzed. Finally, the cross-sectional design precludes establishing causality between antiphospholipid antibodies and endothelial dysfunction, and prospective longitudinal studies are warranted to confirm our findings.

Conclusion

Patients with PAPS, who are predominantly young women with a low prevalence of conventional atherosclerotic risk factors, were found to have ED more frequently than the healthy population. These findings suggest that endothelial impairment in PAPS may be driven primarily by autoimmune mechanisms rather than by traditional risk factors. In this context, strict control of modifiable cardiovascular risk factors, together with adequate treatment of the underlying disease aimed at reducing aPL-mediated vascular injury, appears essential for risk reduction. Given the cross-sectional design and limited sample size of this study, our results should be interpreted with caution; however, they support the rationale for for earlier involvement of a cardiologist, and a multidisciplinary approach in the long-term management of PAPS patients.

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Sažetak

Endotelna disfunkcija izražena kroz dilataciju brahijalne arterije izazvane protokom kod pacijenata sa primarnim antifosfolipidnim sindromom

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Uvod: *Primarni antifosfolipidni sindrom (PAFS) je retka autoimuna bolest koja se karakteriše arterijskim/venskim trombozama i/ili akušerskom patologijom u prisustvu antifosfolipidnih antitela (aFL). Postoje dokazi da aFL direktno deluju sa fosfolipidima membrana endotelnih ćelija, dovodeći do endotelne disfunkcije (ED) i ubrzanja ateroskleroze.*

Metod: *Cilj rada bio je utvrditi zastupljenost ED, iskazane smanjenjem procenta protokom izazvane dilatacije brahijalne arterije (FMD), u kohorti 100 srpskih bolesnika sa PAFS, a bez prethodno dijagnostikovanog kardiovaskularnog oboljenja. Svi ispitanici su prošli kliničku evaluaciju radi detekcije standardnih aterosklerotskih faktora rizika. Analizirana aFL obuhvatala su: lupus antikoagulans (LA), antikardiolipinska antitela (aKL IgG/IgM) i anti-ß2-glikoprotein-I antitela (a-ß2GPI IgG/IgM). FMD je meren nakon standardne pripreme bolesnika i dobijeni rezultati poređeni su sa kontrolnom grupom od 80 zdravih ispitanika.*

Rezultati: *Kohortu PAFS bolesnika dominantno su činile žene starosti 47.7±8.5 godina sa niskom prevalencom standardnih aterosklerotskih faktora rizika. ED, izražena nižim vrednostima FMD, zabeležena je kod 37.6% PAFS bolesnika što je značajno više nego u kontrolnoj grupi (p=0.0001). Starost (p=0.041) i vrednost glikemije (p=0.045) pokazale su statistički značajnu povezanost sa postojanjem ED, što nije bio slučaj sa tipom aFL i kliničkim manifestacijama PAFS. Multivarijantnom regresionom analizom koja je obuhvatila starost, vrednost glikemije i prisustvo tromboza u PAFS nije se izdvojio nezavisan prediktor razvoja ED u PAFS.*

Zaključak: *Endotelna disfunkcija je značajno prisutnija u PAFS bolesnika u odnosu na zdravu populaciju i direktna je posledica autoimunskog procesa. Rano uključivanje kardiologa i adekvatan terapijski pristup mogu smanjiti rizik od budućih kardiovaskularnih komplikacija.*

Ključne reči: *primarni antifosfolipidni sindrom; endotelna disfunkcija; kardiovaskularni rizik*