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Myocardial Ischaemia, Coronary Atherosclerosis and Pulmonary Pressure Elevation in Antiphospholipid Syndrome Patients*

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Abstract

Background. Thrombotic events in antiphospholipid syndrome (APS) involve venous and arterial circulation with the possible involvement of coronary or pulmonary microcirculation.
Objectives. To evaluate the influence of antiphospholipid antibodies (aPL) and on myocardial ischaemia assessed by single-photon emission computerized tomography (SPECT), coronary atherosclerosis assessed by multidetector computerized tomography (MDCT) and pulmonary pressure assessed by transthoracic echocardiography (TTE) in patients with primary antiphospholipid syndrome (PAPS).
Material and Methods. TTE, SPECT (Tc 99m sestamibi) and MDCT-based coronary calcium scoring were performed in 26 consecutive PAPS patients (20 females, 6 males, aged 20–61, mean 39.7) without any signs of other autoimmunological disease and without clinical symptoms of heart disease.
Results. Out of 26 patients, TEE showed normal left and right ventricle function in 25 (96.2%) and elevated (≥ 30 mm Hg) right ventricle systolic pressure in 7 (26.9%) patients. SPECT revealed myocardial perfusion defects in 15 (57.7%) patients: exercise-induced in 6 (23.1%) and persistent in 11 (42.3%). MDCT revealed coronary calcifications in 4 (15.4%) patients. The number of plaques ranged from 1 to 11 (median 2), volume 3–201.7 mm^3 (median 7), calcium scores 1.3–202.6 (median 5.7). In the group with perfusion defects or coronary calcifications (n = 15), all the patients showed elevated aCL IgG.
Conclusions. In most of the relatively young APS patients, without any symptoms of ischemic heart disease, SPECT showed myocardial perfusion defects, and coronary calcifications in 1/6 of them. Right ventricle systolic pressure was elevated in 1/4 of APS patients. These pathologies, well known as cardiovascular risk markers, were associated with elevated levels of the IgG class of both anti-cardiolipin and antiB2 GPI antibodies. Thus, in a high percentage of APS patients, clinically silent myocardial ischaemia, pulmonary pressure elevation and coronary atherosclerosis are present and related to the presence of antiphospholipid antibodies (**Adv Clin Exp Med 2016, 25, 6, 1199–1205**).

Key words: antiphospholipid syndrome, anti-cardiolipin antibodies, anti-beta 2 glycoprotein I antibodies, pulmonary arterial pressure, myocardial ischaemia.

Antiphospholipid syndrome (APS) is an autoimmune multisystem disease of acquired hypercoagulability characterized clinically by recurrent venous and arterial thrombosis, recurrent fetal losses, and serologically by the presence of antiphospholipid antibodies (aPL), including anti-

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cardiolipin (aCL) and antiβ2-glycoprotein I GPI (antiβ2-GPI) antibodies as well as positive lupus anticoagulant [1].

Thrombotic events in APS involve venous and arterial circulation with the possible involvement of coronary or pulmonary microcirculation. This may influence myocardial function and pulmonary vascular resistance and pressure. The prothrombotic action of aPL may share a few common pathways with atherosclerosis [2]. Early clinical observations have suggested that aPL may contribute to the development of atherosclerosis in systemic lupus erythematosus and also in primary APS (PAPS). Increased levels of aPL have also been detected in young/middle-aged patients who suffer from accelerated atherosclerotic disease [3–5]. However, little is known about the objective signs of atherosclerosis development in APS. Asymptomatic atherosclerosis as assessed by ultrasonography occurs in 15% of APS patients compared to 3% in normal controls [6]. In the Euro-Phospholipid cohort of 1000 APS patients, myocardial infarction appeared in 5.5% during the course of the disease [7].

However, considering the low sensitivity of clinical symptoms and electrocardiography (ECG) for the diagnosis of past acute coronary syndromes, the real prevalence of MI in APS might probably be higher. For example, using more advanced methodology (cardiac magnetic resonance imaging), silent myocardial ischaemia was found in 29.6% of APS patients [8].

The present study was conducted to evaluate cardiac involvement in PAPS and the possible influence of antiphospholipid antibodies and lupus anticoagulant on heart pathologies.

Material and Methods

The study was performed in 26 consecutive patients treated for PAPS in the Department of Internal Medicine, Jagiellonian University Medical College, Krakow.

All patients met the Sydney Classification criteria for APS [1]. Exclusion criteria included: pregnancy or lactation at the time of the study and known hypersensitivity to any of the substances used during the study. All patients were in stable clinical condition and at least 12 months after the last venous/arterial thrombosis or fetal loss episode.

In all the patients, SPECT studies (ECAM Gamma Camera, Siemens, Germany) at rest and during exercise (2-day protocol) were performed. On the first day, at near maximal stress, a 25–40 mCi dose of Tc-99m sestamibi was injected (actual patient dose was modified taking into account the patient's weight) and exercise continued for 1 additional minute after injection. Tc-99m sestamibi SPECT imaging was begun 15–30 min later. On the second day, rest examinations were performed. SPECT was performed using a circular 180° acquisition for 60 projections at 20 s per projection. Myocardial perfusion was assessed in 17 left ventricle myocardial segments. The number of segments with rest (persistent) or exercise-induced perfusion defects were assessed by visual interpretation by analyzers blinded for all other information.

Coronary calcium scoring was performed using a multidetector CT imager (Somatom Definition, Siemens, Germany). The images were ECG triggered. The 3-millimeter-thick sections were obtained covering the whole heart. Coronary artery calcifications were defined as lesions with attenuation greater than 130 HU in more than four adjacent pixels. For quantification of the coronary calcium, the 3D Leonardo application (Siemens, Germany) was used. The number of atherosclerotic plaques in particular coronary arteries and its volume were assessed. The Agatson calcium score was calculated [9].

Standard laboratory tests were performed, included fasting glucose and cholesterol level, creatinine concentration, transaminase activity and CRP level. aCL and aβ2GPI were determined in the patients sera using QUANTA Lite® aCL and β2GPI (IgG and IgM) tests [Inova Diagnostics, San Diego, USA. The QUANTA Lite aCL assays report results in GPL and MPL units, and the QUANTA Lite β2GPI assays report results in standard IgG and IgM units (SGU and SMU, respectively)]. All QUANTA Lite ELISAs were performed according to the manufacturer's guidelines.

Lupus anticoagulant (LA) was determined in a three-step procedure according to the guidelines of the ISTH. Diluted Russell's viper venom time (dRVVT; LA1-screen; Siemens, Germany) and a sensitive activated partial thromboplastin time (PTT LA; Diagnostica Stago, France) were used for screening purposes, whereas LA2-confirm (Siemens, Germany) and Staclot LA (Diagnostica Stago, France) were run as confirmatory tests. Reference values for each test were established using the 99^{th} percentile of the healthy population [10].

Statistical analysis was performed using STATISTICA Six Sigma software. All numerical data was expressed as mean values standard deviation, medians or as proportions. Continuous variables were compared by use of a t-test. The χ^2 test was used to examine differences in proportions. The level for statistical significance was predetermined at $p < 0.05$.

Before the study, informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by Ethical Committee of the Jagiellonian University in Krakow.

Results

In the group of 26 patients examined, 20 were female, 6 male, aged 20–61 (mean age 39.7 years). One patient had a history of an objectively confirmed pulmonary embolism. None of the patients had a prior history of coronary artery disease. None of the patients had the classic risk factors for coronary artery disease. ECG recordings were normal in all the patients. Laboratory results showed that out of 26 patients studied, 4 were single-positive (one type of the antiphospholipid antibody present), 5 double-positive, and 17 triple-positive.

Echocardiography showed normal left and right ventricle function in 25 (96.2%) patients (left ventricle ejection fraction 45–75%, mean 63.95%). In 2 (7.7%) patients, mild mitral insufficiency was diagnosed. In 7 (26.9%), tricuspid insufficiency was present with the elevation of right ventricle systolic pressure ≥ 30 mm Hg (RVSP 31–40 mm Hg, mean 36.1 ± 3.2 mm Hg). SPECT revealed myocardial perfusion defects in 15 (57.7%) patients: exercise-induced in 6 (23.1%), persistent in 11 (42.3%). MDCT revealed coronary calcifications in 4 (15.4%) patients. The number of plaques ranged from 1 to 11 (median 2), volume 3–201.7 mm^3 (median 7 mm^3), calcium scores 1.3–202.6 (median 5.7).

In patients with elevated right ventricular systolic pressure (n = 7) all had elevated IgG class aCL and the majority showed the presence of LA and elevated IgG anti-β2-GPI (Table 1).

The percentage of out-of-range immunological results in patients without RVSP elevation was lower as compared to the patients with RVSP ≥ 30 mm Hg, however the difference was not statistically significant (Table 1).

In the group with perfusion defects or coronary calcifications (n = 15), all the patients had elevated IgG class aCL and, 66.7% had elevated IgG class antiβ2-GPI, and LA was present in 86.7% of them (Table 2). The percentage of out-of-range immunological results in patients without myocardial perfusion defects and with no coronary calcifications was lower, however the difference was again not statistically significant (Table 2).

SPECT or MDCT showed pathologies in 1 (25%) single-positive patient, 3 (60%) double-positive patients and 11 (64.7%) triple-positive patients. There were no single-positive patients with RVSP elevation (Table 3).

Fig. 1 shows the examples of coronary calcifications and myocardial perfusion defects observed in a patient with elevated aPL levels.

Discussion

The major finding of this study was the high frequency of left ventricle myocardial perfusion defects and the elevation of right ventricle systolic pressure in a high percentage of APS patients.

The previous data showing myocardial perfusion defects in autoimmune diseases referred mainly

Table 1. The levels of aPL and LA positivity in the examined patients according to right ventricular systolic pressure (RVSP)

Type of antiphospholipid antibodies	RVSP normal n = 19		RVSP > 30 mm Hg n = 7	
	mean ± SD	number (%) of patients with levels out of range	mean ± SD	number (%) of patients with levels out of range
aCL IgG [RU/mL]	51.4 ± 40.9	17 (89.5%)	70.0 ± 48.8	7 (100.0%)
aCL IgM [RU/mL]	40.5 ± 59.6	8 (42.1%)	26.3 ± 15.5	5 (71.4%)
antiβ2GPI IgG [RU/mL]	42.8 ± 54.9	11 (57.9%)	60.3 ± 46.6	5 (71.4%)
antiβ2GPI IgM [RU/mL]	55.6 ± 102.8	7 (36.8%)	13.0 ± 16.3	1 (14.3%)
LA	–	15 (88.2%)	–	6 (85.7%)

aCL – anticardiolipin antibodies (cut-off value for IgG > 20 RU/mL, for IgM > 30 RU/mL; see methods); antiβ2GPI – antiβ2-glycoprotein I antibodies (cut-off value for IgG > 3 RU/mL, for IgM > 2.6 RU/mL; see methods); LA – lupus anticoagulant.

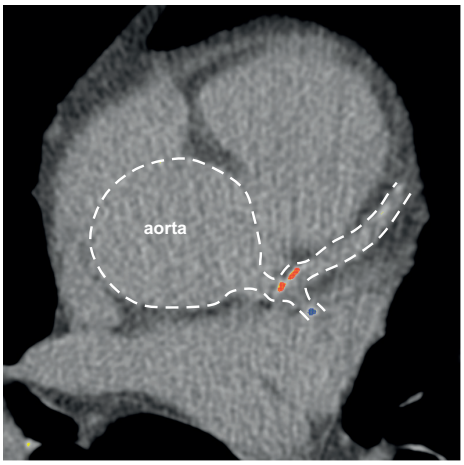
Table 2. Levels of aPL and LA positivity in the examined patients according to myocardial perfusion and coronary calcium deposits

Type of antiphospholipid antibodies	SPECT (–) and CT (–) n = 11		SPECT (+) or CT (+) n = 15	
	mean ± SD	number (%) of patients with levels out of range	mean ± SD	number (%) of patients with levels out of range
aCL IgG [RU/mL]	44.6 ± 40.7	9 (81.8%)	65.1 ± 43.8	15 (100.0%)
aCL IgM [RU/mL]	42.8 ± 68.7	5 (45.5%)	32.2 ± 36.3	8 (53.3%)
antiβ2GPI IgG [RU/mL]	41.3 ± 57.6	6 (54.5%)	52.1 ± 49.9	10 (66.7%)
antiβ2GPI IgM [RU/mL]	68.4 ± 126.6	4 (36.4%)	26.3 ± 49.9	4 (26.7%)
LA	–	8 (72.7%)	–	13 (86.7%)

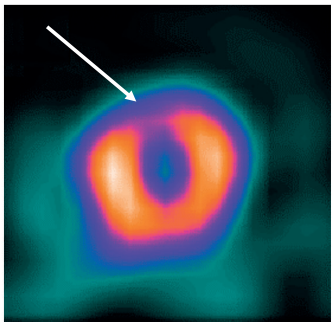
aCL – anticardiolipin antibodies (cut-off value for IgG > 20 RU/mL, for IgM > 30 RU/mL; see methods); antiβ2GPI – antiβ2-glycoprotein I antibodies (cut-off value for IgG > 3 RU/mL, for IgM > 2.6 RU/mL; see methods); LA – lupus anticoagulant.

Table 3. Number of patients with elevated right ventricular systolic pressure (RVSP), myocardial perfusion defects (SPECT +) or coronary calcium deposits (CT +) according to laboratory findings

Positivity	Number (%) of patients with RVSP > 30 mm Hg	Number (%) of patients with SPECT (+)	Number (%) of patients with CT (+)
single (n = 4)	0 (0.0%)	1 (25.0%)	1 (25.0%)
double (n = 5)	3 (60.0%)	3 (60.0%)	1 (20.0%)
triple (n = 17)	4 (23.5%)	11 (64.7%)	2 (11.8%)



In MDCT study, 2 calcified plaques are present in left anterior descending artery (red color) and 1 calcified plaque in circumflex artery (blue color). Plaque volume 156.4 mm^3, calcium score 138.9.



In SPECT study, perfusion defect is present in anterior wall of left ventricle (arrow).

Fig. 1. Examples of MDCT (above) and SPECT (below) results in a patient with elevated aCL IgG (26.11 RU/mL), elevated antiβ2GPI IgG (3.66 RU/mL) and positive lupus anticoagulant test

to systemic lupus erythematosus (SLE) [11–13] or rheumatoid arthritis (RA) [14]. There is only a single study referring to PAPS. In SLE, perfusion defects were detected in 36–38% of asymptomatic patients [14, 15], and when assessed globally in autoimmune diseases (such as SLE, RA and PAPS) it was slightly lower, 27% [13], despite normal rest ECG recordings and lack of myocardial ischaemia clinical symptoms. To the best of our knowledge, this is the first study which shows such a high frequency of myocardial perfusion defects in relatively young PAPS patients who were free from classic risk factors and symptoms of ischemic heart disease. We found perfusion disturbances in 57.7% of the patients examined. The abnormalities were predominantly observed at rest, indicating persistent myocardial injury. It has to be stressed that perfusion defects revealed by SPECT strongly affect the prognosis in non-autoimmune populations [16, 17].

We found only two studies that assessed myocardial perfusion in PAPS patients. In the first, involving 18 patients with PAPS and using (13) N-ammonia positron emission tomography, the authors showed the presence of myocardial ischaemia in 38.8% (7/18) of their patients [18]. This study referred to older patients and a greater proportion of males as compared to our patients. The second study, of 11 PAPS patients, revealed heart perfusion defects in 30% of them by using contrast echocardiography and sestamibi spectrometry. None of these studies analyzed right ventricle systolic pressure.

Right ventricle systolic pressure elevation may form a second factor influencing the prognosis in APS patients. Data from the literature suggests that in autoimmune diseases even slight changes in pulmonary circulation lead to a significant decrease in physical activity capacity [19]. Thus, even slightly elevated (30–40 mm Hg) right ventricle systolic pressure, observed in 1/3 of our patients, may be prognostically important. This is the first report showing a high frequency of RVSP elevation in a stable, otherwise unselected group of APS patients. In the patients with RVSP elevation, all were IgG class aCL-positive and 71.4% had elevated IgG class antiβ2-GPI (the frequency of IgG class antiβ2-GPI-positivity in the normal RVSP group was 57.9%). Recently, Cefle et al. [20] showed a higher frequency of aCL positivity in 10 SLE patients with pulmonary hypertension as compared to 97 SLE patients with normal pulmonary pressure, but in that study, echocardiography was performed only in patients with clinical or radiological symptoms suggesting pulmonary involvement. However, the precise levels of aCL were not reported.

In another study, of 39 mixed connective tissue disease patients, the presence of pulmonary hypertension was associated with higher levels of antiβ2GPI antibodies [21]. Interestingly, SPECT examination also revealed an association between elevated levels of aCL IgG and antiβ2GPI IgG antibodies and myocardial perfusion abnormalities. It is tempting to speculate that the perfusion defects might have been a result of endotheliopathy with microangiopathy caused by small, otherwise undetected thrombi formed in the coronary microcirculation, which in turn have led to the perfusion defects at rest in several small regions of the left ventricle myocardium. Of note, we never observed a pattern characteristic of classic coronary artery disease due to closed large epicardial artery, which typically manifests by larger, sharp-edged defects in the region supplied by a particular coronary artery. Quite a similar mechanism may be involved in aPL-associated pulmonary pressure elevation; namely microembolism/thrombosis of pulmonary microcirculation resulting in increased pulmonary resistance with RV systolic pressure elevation. A parallel mechanism may also involve intimal proliferation similar to that described in kidney microcirculation [22]

Besides the presence of myocardial perfusion abnormalities and right ventricle pulmonary pressure elevation, 15.4% of our asymptomatic APS patients manifested atherosclerosis in coronary arteries. Coronary vessels are most frequently affected by calcifications in autoimmune diseases. In a study of 50 SLE patients [23], high frequency of atherosclerotic plaques as shown by MDCT was observed in coronary arteries (42% of patients with calcifications), followed by carotid arteries (24% of patients with calcifications). The frequency of coronary calcifications in our APS group was lower than that reported in SLE. Still, coronary calcium deposits provide independent prediction of short- and long-term cardiac events [24, 25]. Even in patients with normal SPECT results, an increased coronary calcium score identifies subjects at high long-term cardiac risk [24]. Antiphospholipid antibodies may initiate or exacerbate the process of lipid deposition and plaque formation. Among antiphospholipid antibodies, a crucial role in the pathogenesis of atherosclerosis is attributed to aCL antibodies and antiβ2GPI antibodies [26, 27].

Our results may also have implications for the management of APS patients. The presence of atherosclerotic plaques and myocardial perfusion defects in a SPECT study are strong predictors of death [16, 17, 24, 25]. The mechanism of these abnormalities, in which microthrombosis might play a major role, should direct our attention to thrombosis prevention. Generally, in APS patients without clinically observable venous or arterial thrombosis, anticoagulation is not recommended, despite

the aPL titers. However, it was reported that in asymptomatic aCL-positive patients, thrombo-prophylaxis with aspirin or low-molecular weight heparin during high-risk periods (surgery, immobilization) is effective at reducing thrombotic complications [28]. Among asymptomatic aCL-positive SLE patients, primary prophylaxis with aspirin and hydroxychloroquine also reduced the frequency of thrombotic events [29]. The value of antithrombotic treatment on perfusion abnormalities, pulmonary arterial pressure and coronary calcification formation, and as a consequence on the prognosis of APS patients, should be addressed in large prospective clinical trials.

In conclusion, in most relatively young APS patients, SPECT shows myocardial perfusion defects with coronary calcifications present in 1/6 of them. Right ventricle systolic pressure is elevated in 1/4 of APS patients. These pathologies, well-known as cardiovascular risk markers, are combined with elevated levels of anticardiolipin and antiβ2-GPI antibodies of the IgG class. Thus, in a high percentage of APS patients, clinically silent myocardial ischaemia, pulmonary pressure elevation and coronary atherosclerosis are present, and causally related to the presence of antiphospholipid antibodies. The value of antithrombotic treatment on perfusion abnormalities, pulmonary arterial pressure and coronary calcification formation, and as a consequence on the prognosis of APS patients, should be addressed in large prospective clinical trials.

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