The adjunctive role of antiphospholipid antibodies in systemic lupus erythematosus cardiac involvement

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Abstract

Objective

To evaluate the prevalence of cardiac alterations by trans thoracic echocardiography (TTE) and the possible role of aPLs in determining heart damage in SLE patients.

Patients and methods

We investigated 34 consecutive Caucasian SLE patients and 34 age and sex- matched controls. All patients underwent TTE. Lupus anticoagulant (LA) was assayed. IgG and IgM antiphospholipid antibodies against cardiolipin (aCL), phosphatidylinositol (aPI), phosphatidylserine (aPS), phosphatidic acid (aPA), and anti-β2-glycoprotein I antibodies (aβ2GPI) were determined by ELISA.

Results

Nineteen (56%) SLE patients showed at least one cardiac abnormality (P < 0.0001 – RR 19; OR 41.8; 95% CI 5.1-342). The predominant valve dysfunctions were represented by mitral (21%) and tricuspidal (18%) regurgitation. Aortic regurgitation was observed in 12% of patients, pericardial effusion and left atrial enlargement were identified in 15% and 12% of cases, respectively. Mitral valvular strands were detected in one patient. The prevalence of cardiac abnormalities correlated with disease duration. Echocardiographic alterations were more common in aPLs positive than in aPLs negative patients (P = 0.02 – RR 2.5; OR 6.1; 95% CI 1.2-30.1). Patients with IgG-aPA, -aPI and -aPS had a higher prevalence of left atrial enlargement (P < 0.05); IgG-aPA and -aPI were significantly associated with increased interventricular septum thickness (P < 0.05).

Conclusions

Our findings confirm that the heart is one of the main target in SLE patients. The association between aPLs and cardiac impairment suggests an adjunctive role of these autoantibodies in determining heart damage. SLE vasculopathy is a multifactorial process leading to accelerated atherosclerosis. Heart involvement over the course of disease requires a comprehensive screening and management of traditional and new cardiovascular risk factors to prevent cardiac damage, which represents the primary cause of morbidity and mortality in SLE patients.

Key words

Systemic lupus erythematosus, valvular heart disease, transthoracic echocardiography, antiphospholipid antibodies.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, inflammatory autoimmune disease that can affect any and every organ system of the body.

During the last two decades many authors have focused their attention on cardiac involvement and its multifactorial pathogenesis over the course of SLE. Cardiac impairment represents one of the main causes of morbidity and mortality in SLE patients. It is characterized by a pancarditis involving the pericardium, myocardium, endocardium and coronary arteries, and very commonly resulting in valvular impairment (1). Most patients do not have clinically symptomatic valvular dysfunction even if heart failure, thromboembolism and secondary infective endocarditis might occur or valve replacement is required.

Antiphospholipid antibodies (aPLs) are a family of autoantibodies that exhibit a broad range of target specificities and affinities, all recognizing various combinations of phospholipids, phospholipid-binding proteins, or both, clinically associated with a thrombophilic disorder named antiphospholipid syndrome (APS) (2-5).

Moreover, aPLs have also been related to SLE clinical manifestations defining the most frequent form of secondary APS (6, 7).

Anticardiolipin antibodies (aCL) have been the most extensively studied aPLs. In recent studies the prevalence and clinical relevance of autoantibodies against other negatively charged phospholipids such as antiphosphatidylserine (aPS) and antibodies to β2-glycoprotein I (aβ2GPI), a plasma protein with anticoagulant activities, have been revaluated (5, 8, 9).

Since the '90s, a significant higher prevalence of valvular involvement was observed in patients with APS secondary to SLE, suggesting a possible association between aPLs and heart injury (7). However, many studies documented a similar prevalence of valve abnormalities in patients with and without these autoantibodies (10, 11). Furthermore, no studies have been performed to examine the association between heart damage and a various combination of aPLs.

The aim of our study was to evaluate the prevalence of cardiac alterations detectable by trans thoracic echocardiography (TTE) and the possible role of aPLs in determining heart damage in patients with SLE.

Patients and methods

Thirty-four consecutive Caucasian SLE patients (28 women, 6 men; mean age 38 ± 13 years, disease duration 7 ± 4 years) being treated in our department were enrolled in this study. A control group of 34 age- and sex-matched healthy volunteers was included in the study.

All SLE patients fulfilled four or more criteria of the American College of Rheumatology (ACR) for the classification of SLE (12), updated according to Hochberg (13). Seven out of 34 SLE patients fulfilled the 1999 Sapporo consensus classification criteria for APS updated according to the International Consensus statement on the classification criteria for definite APS (2, 3).

A written informed consent was provided by all patients.

Table I reports the main clinical characteristics and cardiovascular risk factors of the enrolled population. Patients with previous rheumatic fever, history of cancer and/or drug abuse were excluded. Moreover, in order to assess properly Lupus Anticoagulant (LA), patients treated with oral anticoagulant have been excluded (14).

Physical examination, blood collection and a Doppler echocardiographic study was performed at the same time. Sera were stored at -80°C until assayed.

Doppler transthoracic echocardiography

Transthoracic Doppler Echocardiographic (TTE) examinations were carried out by a single examiner. M-mode and two-dimensional echocardiography with spectral and color flow Doppler analysis were performed using an ultrasound machine (Sonos 2500, Hewlett Packard, Andover, MA), with a 2.5- or 3.5-mHz transducer. All patients were examined in the left lateral decubitus position and data were obtained during post-expiratory apnea.

Table I. Main features and cardiovascular risk factors of the studied population.

	SLE patients (n. 34)	Controls (n. 34)
Age, years, mean ± SD (range)	38 ± 13 (15-67)	42 ± 5 (38-60)
Gender (F/M)	28 / 6	28 / 6
BMI, Kg/m^2, mean (range)	24 ± 5 (15-34)	24 ± 4 (18-34)
BMI > 25 (%)	13 (38.2)	12 (35.3)
Smoking, >10 cig./day (%)	7 (20.6)	9 (26.5)
Hypertension, sP>140 mmHg and/or dP>90 mmHg (%)	12 (35.3)	3 (8.8)
Hyperlipidemia, tot.col.>200mg/dl, HDL<45mg/dl, LDL >130 mg/dl (%)	8 (23.5)	6 (17.6)
Diabetes (%)	1 (2.9)	0
Higher creatinine, >1.5mg/dl (%)	6 (17.6) *	0
Hyperhomocysteinemia, > 15 UI/ml (%)	12 (32.3) *	4 (11.7)
Age at diagnosis, years, mean ± SD (range)	30 ± 12 (18-55)	
Disease duration, years, mean ± SD (range)	7 ± 4 (1-16)	
Patients: SLE/SLE + APS (n.)	27 / 7	
Treatment:		
None (%)	3 (8.8)	
CCS (%)	15 (44.1)	
CCS + hydroxycloroquine (%)	6 (17.6)	
CCS + CTX (%)	3 (8.8)	
CCS + CyA (%)	3 (8.8)	
CCS + CyA + CTX (%)	2 (5.9)	
NSAIDs / ASA (%)	3 / 7 (8.8 / 20.6)	

ASA: acetylsalicylic acid; CCS: corticosteroids; CTX: cytotoxic immunosuppressor; CyA: cyclosporine A; NSAIDs: non-steroidal anti-inflammatory drugs

* $P < 0.05$

Images were recorded on a super-VHS videotape and analysed by two independent observers. Echocardiographic data were calculated as mean values of three measurements of the cardiac cycle. Standard left parasternal long and short axis and apical two-, four-, and five-chamber views were performed in all patients (15).

The following morphological parameters were analysed: left (LAt) and right (RAt) atrial diameters, left ventricular end diastolic (LVDD) and systolic (LVSD) diameters, right ventricular end diastolic diameters (RVDD), and left ventricular ejection fraction (EF%), calculated using the area-length method.

By using the spectral Doppler approach the systolic function was evaluated by the following parameters: pre-ejection period (PEP), left ventricular ejection time (LVET) and their ratio (PEP/LVET). The diastolic function was assessed by analysing the mitral flow velocity curves: the peak flow velocity in early (E) and late (A) diastole, and their ratio (E/A), the deceleration time of E wave, and the duration of atrial contraction (ms) (16).

The pulmonary venous flow pattern was assessed by analysing the peak velocity of systolic, diastolic and atrial component flows.

The pulmonary systolic arterial pressure (PSAP) was estimated in patients with tricuspid regurgitation by adding 10 mmHg to the systolic gradient (4 x peak velocity^2) between the right ventricle and right atrium. The cardiac output (CO), the stroke volume (SV), the cardiac index (CI), and the peripheral vascular resistance (PVR) were calculated by applying the following formulae: CO = SV x HR (heart rate); SV = (left ventricular outflow tract area) x (mean blood velocity across the aortic valve) x (ejection time); CI = CO/BSA (body surface area); PVR = (MAP x 80)/CO.

Valvular impairment was analysed by Doppler evaluation and the results were expressed as semi-quantitative data. Valve alterations have been considered for the purpose of the study only when haemodynamically relevant.

Antiphospholipid determination

Detection and characterization of IgG and IgM antiphospholipid antibodies isotypes were carried out by enzyme linked immunosorbent assay (ELISA) using commercially available kits (ORGenTec-Diagnostika GmbH, Mainz, Germany).

Sera were firstly screened on microplates coated with a mixture of highly purified negatively charged phospholipids, i.e., cardiolipin, phosphatidylserine, phosphatidylinositol and phosphatidic acid (Anti-Phospholipid Screen IgG/IgM; ORG 529 - ORGenTec-Diagnostika).

All samples were analysed in duplicate. One hundred milliliters of calibrators and sera from patients and controls diluted 1:100 were added to the wells. After a 30-minute incubation at 25 °C, microplates were washed three times with wash buffer. Then, 100 µl of horseradish peroxidase conjugate rabbit antihuman IgG or IgM were added. After a 15-minute incubation, plates were extensively washed and a chromogenic substrate solution containing 3, 3', 5, 5'-tetramethyl-benzidine was dispensed into the wells. Following a 15-minute incubation in the dark, color development was stopped by adding 100 µl/well of 1-M hydrochloric acid. The optical density (OD) was read at 450 nm using Grailis Advanced Reader (Bouty, Milan, Italy). As indicated by the company, this assay system is calibrated against the internationally recognized aCL reference sera from Harris E.N. (17). A standard curve was established by the above mentioned combined calibrators with IgG and IgM antibodies. Values ≥ 10 arbitrary units/ml (U/ml) were considered positive, after this preliminary screen. This cut-off was higher than the 99th percentile of 60 control sera for both IgG and IgM antibodies.

Sera positive in the screening were tested against single phospholipid antigens coated in the presence of β2-GPI as cofactor or against highly purified β2-GPI, which was coated on high binding γ-irradiated wells (ThromboCombo, ORGenTec-Diagnostika). ELISA was performed as for the screening test. Sera showing OD values exceeding the detection limit of the standard curve were further diluted and assayed.

Because reference sera for antiphosphatidic acid (aPA), antiphosphatidilinositol (aPI), antiphosphatidilserine (aPS) and anti β2-GPI (aβ2-GPI) are not available, the assay for these antibodies was arbitrary calibrated utilizing aCL reference sera.

According to Harris (18, 19), IgG-aCL or IgM-aCL values between 10 and 20 U/ml were considered low positive, whereas values ≥ 20 U/ml were taken as medium-high positive.

Lupus anticoagulant (LA) was assayed following the recommendations of the International Society of Thrombosis and Haemostasis (20). Screening assays included the kaolin clotting time, dilute APTT, dilute PT, and 2 dilute Russell viper venom times; all tests were repeated in a 1:1 mix with normal plasma, and positive test results were confirmed with the same reagent in the presence of excess phospholipids. At least one test system result had to be positive in all steps for a patient to be considered LA positive.

Antiphospholipid syndrome was defined according to Sapporo criteria updated to International consensus statement on the classification criteria for definite APS (2, 3).

Statistical analysis

Data were analysed using the Prism statistical package (Graphpad Instat, version 3). Categorical variables were compared using Fisher exact's test. Continuous variables were analyzed by the Student t-test and Mann Whitney U-test for parametric and nonparametric data, respectively. Relative Risk (RR), Odds Ratio (OR) and 95% Confidence Interval (CI) were calculated using standardized methods. P-value < 0.05 was considered significant.

Results

All patients underwent physical examination: three SLE patients presented muffled heart sounds and one systolic murmur at heart auscultation. All controls had normal cardiac examination.

SLE related clinical manifestations and laboratory findings are summarized in Table II.

Nineteen SLE patients (56%), asymptomatic for ischemic coronary events, showed at least one alteration by echocardiography as compared to the control group (3%) (P < 0.0001; RR 19; OR 41.8; 95% CI 5.1-342) (Fig. 1a).

In SLE cohort the ejection fraction (EF) was 61 ± 6 % vs 66 ± 7 in the control group (mean ± SD) (P < 0.001). Two patients with SLE (6%) had severely compromised systolic function (EF < 45%). Systolic or diastolic hypertension was detected in 12 cases (35.3%). Moreover, in 2 patients (6%) pulmonary systolic arterial pressure (PSAP) was > 25 mmHg (Table III).

Table II. SLE related clinical manifestations and laboratory findings in our cohort of patients.

		n.	%
Malar rash		19	55.9
Discoid rash		13	38.2
Fotosensibility		22	64.7
Oral ulcers		1	2.9
Serositis		7	20.6
Articular involvement		32	94.1
Renal involvement		12	35.3
Neuropsychiatric involvement		25	73.5
Hematological involvement			
Hb < 12 g/dl		20	58.8
Haemolytic anemia		2	5.9
Leukopenia (WBC < 4,000/mmc)		7	20.6
Lymphopenia (Ly < <1,500/mmc)		4	11.8
Thrombocytopenia (PLT < 100,000/mmc)		6	17.6
Autoantibodies			
ANA		32	94.1
anti-dsDNA		8	23.5
anti-Sm		3	8.8
LA		14	44.1
aCL	*IgM*	8	23.5
	IgG	17	50
aPA	*IgM*	9	26.5
	IgG	12	35.3
aPS	*IgM*	6	17.6
	IgG	14	41.2
aPI	*IgM*	9	26.5
	IgG	13	38.2
aβ2GPI	*IgM*	6	17.6
	IgG	12	35.3
Secondary Antiphospholipid Syndrome		7	20.6
Arterial thrombosis		3	42.8
Venous thrombosis		4	57.1
Pregnancy morbidity		5	71.4

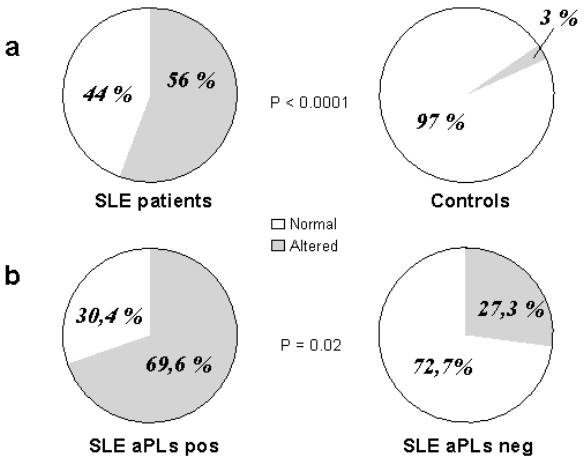

Fig. 1. Overall echocardiographic impairment in our cohort of SLE patients compared to control group.
aPLs: antiphospholipid antibodies;
SLE: systemic lupus erythematosus.

The predominant valve dysfunction in our SLE cohort was regurgitation with a moderate impairment: mitral and tricuspidal alterations were detected in 7 (21%) and 6 patients (18%), respectively, and mitral valvular strands on the ventricular surface in one case (3%). Aortic impairment was observed in 4 patients (12%). Pericardial effusion was identified in 5 (15%) and left atrial enlargement in 4 cases (12%), respectively. The only cardiac alteration in controls was mild mitral regurgitation, detected in one subject (3%) (Fig. 2).

The prevalence of echocardiographic abnormalities in our cohort was associated with disease duration. Cardiac abnormalities were detected in 9 patients (69%) with disease duration ≥ 10 years and only in 3 out of 12 (25%) with a shorter duration (< 5 years) (P = 0.03) (Fig. 3).

Twenty-three SLE patients (67.6%), 7 with APS and 16 without, were positive for LA and/or one among the aPLs (IgM or IgG isotype) antibodies tested. All patients with aβ2GPI, aPA, aPS and aPI -IgG antibodies showed medium-high titre positivity for aCL IgG.

Echocardiographic abnormalities were more common in aPLs positive than in aPLs negative patients (69,6% vs 27,3%) (P = 0.02; RR 2.5; OR 6.1; 95% CI 1.2-30.1) (Fig. 1b).

Lupus anticoagulant was positive in 14 patients (44.1%) and negative in all controls (P < 0.0001). IgM and IgG aCLs were present in 8 (23.5%) and in 17 (50%) SLE patients, respectively, and were absent in the control group (P < 0.01). LA and/or aCL (low and medium-high titre) positivity was not significantly associated with the presence of echocardiographic abnormalities. aPA-IgG antibodies were found positive in 12 cases (35.3%) and were associated with left atrial enlargement (P = 0.01) and increased interventricular septum thickness (P < 0.05). The presence of aPS-IgG antibodies was detected in 14 cases (41.2%) and was associated with left atrial enlargement (P < 0.05). aPI-IgG antibodies, positive in 13 cases (38.2%), were statistically associated with left atrial enlargement (P = 0.01) and increased interventricular septum thickness (P < 0.05). IgM and IgG aβ2-GPI were present in 6 (17.6%) and in 12 SLE patients (35.3%), respectively, in absence of statistical association with echocardiographic findings. (Table IV)

Table III. Echocardiographic findings in SLE patients and controls.

	MEAN ± SD (min – max) SLE patients (n. 34)	Controls (n. 34)	P
Left atrium (LA)	35 ± 5 (27-49)	30 ± 3 (25-37)	< 0.0001
Interventricular septum (IVS)	9 ± 2 (6 -14)	9 ± 1 (2 -11)	NS
Ejection Fraction (EF %)	61 ± 6 (40-71)	66 ± 7 (54-76)	0.001
Mitral insufficiency (MI)	7 (21%)	1(3%)	0.03
Tricuspidal insufficiency (TI)	6 (18%)	0	0.01
Aortic insufficiency (AI)	4 (12%)	0	0.04
Pulmonary insufficiency (PI)	1 (3%)	0	NS
Valvular strands	1 (3%)	0	NS
Pericardial effusion	5 (15%)	0	0.03
LA dilatated	4 (12%)	0	0.04
IVS hypertrophy	3 (9%)	0	NS
EF < 45 %	2 (6%)	0	NS
Diatolic dysfunction	2 (6%)	0	NS
PSAP (> 25 mmHg)	2 (6%)	0	NS

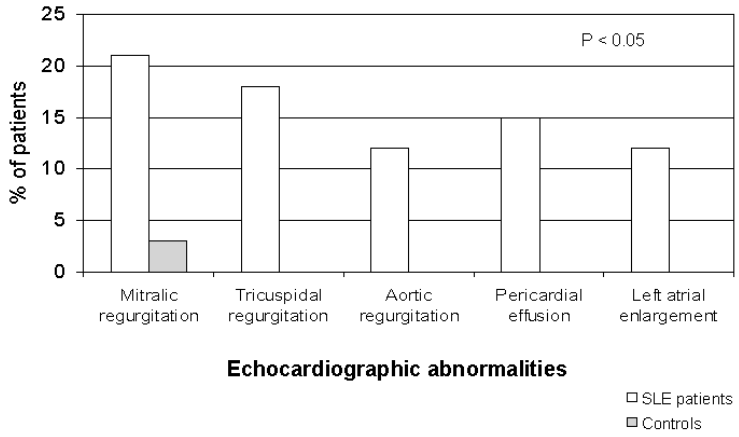

Fig. 2. Echocardiographic abnormalities in SLE patients compared to controls (all differences are statistically significant - P < 0.05)
SLE: systemic lupus erythematosus.

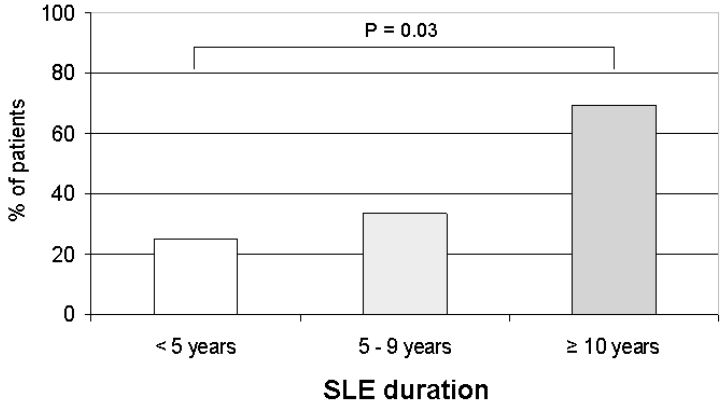

Fig. 3. Echocardiographic abnormalities in SLE patients related to disease duration.
SLE: systemic lupus erythematosus.

Table IV. Association between aPLs positivity and echocardiographic findings in SLE patients.

			MI	TI	AI	PI	Pericardial effusion	Left atrium enlargment	PSAP > 25 mmHg	EF < 50 %	IVS hypertrophy	Diastolic dysfunction
LA		pos *(n = 14)*	4 (29%)	0	3 (21%)	0	3 (21%)	3 (21%)	0	1 (7%)	2 (14%)	1 (7%)
		neg *(n = 20)*	3 (15%)	6 (30%)	1 (5%)	1 (5%)	2 (10%)	1 (5%)	2 (10%)	1 (5%)	1 (5%)	1 (5%)
aCL	*IgM*	pos *(n = 8)*	2 (25%)	2 (25%)	1 (12%)	0	1 (12%)	2 (25%)	0	1 (12%)	2 (25%)	0
		neg *(n = 26)*	5 (19%)	4 (15%)	3 (11%)	1 (4%)	4 (15%)	2 (8%)	2 (8%)	1 (4%)	1 (4%)	2 (8%)
	IgG	pos *(n = 17)*	4 (23%)	4 (23%)	2 (12%)	1 (6%)	3 (18%)	4 (23%)	2 (12%)	1 (6%)	3 (18%)	0
		neg *(n = 17)*	3 (18%)	2 (12%)	2 (12%)	0	2 (12%)	0	0	1 (6%)	0	2 (12%)
aPA	*IgM*	pos *(n = 9)*	2 (22%)	1 (11%)	1 (11%)	0	2 (22%)	2 (22%)	0	1 (11%)	2 (22%)	0
		neg *(n = 25)*	5 (20%)	5 (20%)	3 (12%)	3 (12%)	3 (12%)	2 (8%)	2 (8%)	1 (4%)	1 (4%)	2 (8%)
	IgG	pos *(n = 12)*	4 (33%)	3 (25%)	2 (17%)	1 (8%)	3 (25%)	4 # (33%)	1 (8%)	1 (8%)	3 * (25%)	0
		neg *(n = 22)*	3 (14%)	3 (14%)	2 (9%)	0	2 (9%)	0 #	1 (4%)	1 (4%)	0 *	2 (9%)
aPS	*IgM*	pos *(n = 6)*	2 (33%)	0	1 (17%)	0	1 (17%)	2 (33%)	0	1 (17%)	2 (33%)	0
		neg *(n = 28)*	5 (18%)	6 (21%)	3 (11%)	1 (4%)	4 (14%)	2 (7%)	2 (7%)	1 (4%)	1 (4%)	2 (7%)
	IgG	pos *(n = 14)*	4 (28%)	4 (28%)	3 (21%)	1 (7%)	3 (21%)	4 * (29%)	2 (14%)	1 (7%)	3 (21%)	0
		neg *(n = 20)*	3 (15%)	2 (10%)	1 (5%)	0 *	2 (10%)	0	0	1 (5%)	0	2 (10%)
aPI	*IgM*	pos *(n = 9)*	2 (22%)	0	1 (11%)	0	1 (11%)	1 (11%)	0	1 (11%)	2 (22%)	0
		neg *(n = 25)*	5 (20%)	6 (24%)	3 (12%)	1 (4%)	4 (16%)	3 (12%)	2 (8%)	1 (4%)	1 (4%)	2 (8%)
	IgG	pos *(n = 13)*	5 (38%)	3 (23%)	2 (15%)	0	3 (23%)	4 # (31%)	2 (15%)	1 (8%)	3 * (23%)	0
		neg *(n = 21)*	2 (9%)	3 (14%)	2 (9%)	1 (5%)	2 (9%)	0 #	0	1 (5%)	0 *	2 (9%)
aβ2GPI	*IgM*	pos *(n = 6)*	0	0	0	0	0	0	0	0	2 (33%)	0
		neg *(n = 28)*	7 (25%)	6 (21%)	4 (14%)	1 (4%)	5 (18%)	4 (14%)	2 (7%)	2 (7%)	1 (4%)	2 (7%)
	IgG	pos *(n = 12)*	2 (17%)	1 (8%)	1 (8%)	0	2 (17%)	2 (17%)	1 (8%)	1 (8%)	2 (17%)	0
		neg *(n = 22)*	5 (23%)	5 (23%)	3 (14%)	1 (4%)	3 (14%)	2 (9%)	1 (4%)	1 (4%)	1 (4%)	2 (9%)

AI: aortic insufficiency; EF: ejection fraction; IVS: interventricular septum; MI: mitral insufficiency; PI: pulmonary insufficiency; PSAP = pulmonary systolic arterial pressure; TI: tricuspidal insufficiency.

* $P < 0.05$

\# $P = 0.01$

Discussion

In the past, cardiac abnormalities in SLE were frequently found in post mortem examination. The efficacy of currently treatments has improved the survival of these patients allowing the detection of cardiovascular involvement, less commonly observed before. Nowadays, cardiac impairment can be frequently recognized by echocardiography and other non-invasive tests (1).

It has been reported that by echocardiography, heart abnormalities could be detected in about 70% of SLE patients (21). Data from different studies assessed that valvular involvement represents the main defect identified (ranging from 28% to 74%) and it can occur as vegetations (Libman-Sacks endocarditis), leaflet thickening, valve regurgitation and, rarely, stenosis (7).

By use of TTE, our study showed that at least one cardiac abnormality was present in 56% of SLE patients. As previously reported, valvular affection involves most commonly the left-sided and this datum is in concert with our result. In addition, we found a higher prevalence of atrium-ventricular valves impairment and in other studies it has been demonstrated that the mitral valve was mainly affected (7).

It has been reported a significantly higher prevalence of valvular defects in SLE patients with than in those without aPLs (7) and almost 89% of patients suffering of valvular involvement showed aPLs positivity, compared to 44% of those negative (6, 22, 23).

Noteworthy, the prevalence of valvular involvement was observed more frequently in APS secondary to SLE than in primary APS (7, 24, 25).

Taken together, these data suggest that both aPLs and other SLE-related factors could independently promote endhocardial damage. Although characteristic organ lesion that occurs in PAPS is a vascular occlusion without inflammation (26, 27), over the course of SLE inflammatory immune alterations were found within vessel walls in valvular lesions (28-32).

SLE vasculopathy is known to be characterized by subendhotelial deposits of immunocomplexes and by polymorphonuclear, lymphocyte and mononuclear-cell vessel infiltration (33): the inflammatory immune activation on the vessel wall enhances the local damage chronically leading to the development of atherosclerotic lesions. There are evidence that the same mechanism involves the cardiac valve surface with subsequent platelet adhesion, fibrin deposition and evolution through valvular strands formation (34).

Garcia-Torres *et al.* recognized fibrin deposits as the key factor in endocardium involvement (35). Ziporen *et al.* (28) have shown positive staining for human immunoglobulins and for complement compounds in the subendothelial ribbon-like layer along the surface of the leaflets and cups. All these structural modifications cause fibrosis and a progressive endocardial stroma infiltration induces cardiac wall impairment. The initial valve insult has not been identified yet. Lev and Shoenfeld proposed a direct role of aPLs and complement components in initiating valve damage (7, 36).

In our study, the detection of echocardiographic abnormalities by trans thoracic study was more frequent in aPLs positive than in negative SLE patients (OR = 6.1).

Of note, Toubi *et al.* found an association between valvular impairement detected by TTE and livedo reticularis (LR) in a large cohort of APS patients. This skin manifestation can be a sign of an ongoing chronic endothelial cell damage that affects heart as well as other organs (37).

Three out of our patients (8.8%) presented with this skin vasculopathy but we didn't find a correlation with heart involvement due to the small sample size.

In all patients with aCL-IgG positivity were present all the other subclasses of aPLs tested (aβ2GPI, aPA, aPS and aPI -IgG). This result could indicate a wide cross-reactivity between different aPLs, due to the similarities between other anionic phospholipids and cardiolipin, regarding structure, charge, and configuration (38, 39).

Interestingly, in our cohort of patients, disease duration correlated with the prevalence of ecocardiographic abnormalities, showing a higher impairment in those with a longer disease duration compared to other patients (69% vs 25%), but there were no associations with patients' age. This occurrence could be the end point attributable to a multifactorial process involving the long exposure to traditional as well as new cardiovascular risk factors. Moreover, immunosuppressive drugs and immunological markers (mainly aPLs, anti-ds-DNA and circulating immunocomplexes) cooperate in cardiovascular damage leading to accelerated atherosclerosis.

Other authors did not document correlation between disease duration and heart damage (21, 40), but these studies are difficult to be compared due to the different criteria for patients' stratification.

In conclusion, transthoracic echocardiography represents a useful diagnostic tool for the detection of SLE related cardiac abnormalities. Although transesophageal echocardiography is more sensitive in detecting valvular lesions, trans-thoracic approach has the advantages of being uninvasive, well tolerated and less costly and hence routinely used in the follow-up of SLE patients.

Finally, aPLs autoantibodies and their related complications may be considered a pathogenic factor in SLE vasculopathy. Since this process is multifactorial, heart involvement requires a comprehensive screening of all cardiovascular risk factors (41).

With regard to valve impairment, serial evaluations of SLE patients should be undertaken, searching the presence of aPLs antibodies and performing TTE. Moreover, physicians should look for aPLs presence in patients with valvulopathy not attributable to other causes. The vigorous management of traditional and new cardiovascular risk factors has to be pursued to prevent cardiac damage that, at present, constitutes the primary cause of morbidity and mortality in SLE patients with long term survival (42).

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