Assessment of echocardiographic abnormalities in patients with systemic lupus erythematosus: correlation with levels of antiphospholipid antibodies

Raffaele Gentile, Bruno Laganà, Luigi Tubani, Milvia Casato, Giovanni M. Ferri, Francesco Fedele*

*Department of Clinical Medicine, *Department of Cardiovascular and Respiratory Sciences, "La Sapienza" University of Rome, Rome, Italy*

Key words:
Systemic lupus erythematosus; Antiphospholipid antibodies; Cardiac involvement.

Background. **The aim of this study was to evaluate the incidence of morphologic and functional cardiac abnormalities in patients with systemic lupus erythematosus and correlate the data with antiphospholipid antibody (aPL) levels.**

Methods. **Ninety-one patients with systemic lupus erythematosus were enrolled and divided into two groups according to the presence (Group 1, n = 45) or absence of aPL (Group 2, n = 46). All patients underwent standard two-dimensional and Doppler echocardiographic examination. aPL were detected by a standardized and validated ELISA test. Five patients with regional ventricular dysfunction also underwent coronary angiography. The χ^2 test was used for the statistical analysis of the data. For smaller groups of samples the Fisher's exact test was employed.**

Results. **Pericardial effusion was detected in 19 patients without any statistical difference between the two groups. A valvular involvement was present in 39 patients: a moderate-severe degree was more frequent in Group 1 (p = 0.02). Regional wall motion abnormalities were observed in 8 patients: only 1 in Group 2 and 7 in Group 1 (p = 0.03). Coronary angiography showed normal arteries in all patients of Group 1.**

Conclusions. **aPL play a role in the pathogenesis of the severity of valvular lesions as well as in regional myocardial dysfunction, suggesting a small vessel disease.**

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Address:

Dr. Raffaele Gentile

Dipartimento di Medicina Clinica Università degli Studi "La Sapienza" Viale dell'Università, 37 00185 Roma

Introduction

The cardiovascular system is frequently involved in systemic lupus erythematosus (SLE) and represents an important factor in determining prognosis and outcome. The endocardium, myocardium, pericardium and coronary vessels are involved with a high incidence, as described in clinical and necropsy studies[1-4].

The presence of antiphospholipid antibodies (aPL) is often associated with a syndrome characterized by arterial and/or venous thrombosis, recurrent abortion, and thrombocytopenia[5,6].

This syndrome is often associated with SLE but may also appear as "primary" syndrome. Many studies have investigated the relationship between the presence of aPL and cardiac abnormalities: the majority of authors have supported this association[7-12].

The aim of this study was to describe our experience concerning the incidence and spectrum of morphologic and functional cardiac abnormalities in SLE patients by means of echocardiographic examination and correlate the data with the presence or absence of aPL.

Methods

Study population. In this study we considered prospectively all in- as well as outpatients, fulfilling the revised criteria of the American College of Rheumatology for definite SLE diagnosis[13] (formerly, the American Rheumatism Association), referred to the echocardiographic laboratory between January 1994 and December 1998.

The study group (Group 1) consisted of 45 patients selected on the basis of positivity for aPL: they were further divided into

two subgroups according to the antibody levels: Group 1A (high aPL levels, n = 20) and Group 1B (low aPL levels, n = 25).

Another 46 SLE patients (free from aPL) were enrolled as controls (Group 2): no significant differences were found between these two groups regarding age, sex, blood pressure values, organ involvement, or disease activity assessed by the Systemic Lupus Activity Measure[14]. The main signs, symptoms and laboratory data are summarized in table I.

In addition, a history of thrombosis and/or recurrent fetal loss was present in 23 aPL patients (15 in Group 1A and 8 in Group 1B).

Overall, there were 77 female and 14 male patients, aged 14-60 years (mean 35.2 years), and mean disease duration was 4.5 years (range 2 months-20 years).

These 91 patients were selected from a larger population (n = 109): those aged > 60 years or patients who had a history suggestive of heart disease (such as suspected ischemic or rheumatic heart disease) prior to the development of the clinical manifestation of SLE were excluded from the study.

Echocardiographic examination was performed in the same period (with a range of 2-5 days apart) as the aPL test in hospitalized patients and even on the same day as ambulatory/day-hospital patients. All 91 patients were visited and examined at least twice with a minimum of 3 months apart.

Eight patients with echocardiographically detected wall motion abnormalities were required to undergo a coronary angiography, according to the standard Judkins technique, after informed consent. The invasive examination was accepted by 5 patients and refused by the other 3.

Detection of antiphospholipid antibodies. aPL were detected by a standardized and validated ELISA test as described by Loizou et al.[15] with some modifications. Serum levels of aPL were calculated and expressed as GPL or MPL for IgG and IgM aPL, respectively.

Table I. Clinical and laboratory data of patients with systemic lupus erythematosus.

	aPL positive (%)	aPL negative (%)
SLAM*	15.2 (range 3-28)	12.7 (range 6-26)
Malar rash	26 (57.7)	21 (45.6)
Discoid rash	5 (11.1)	7 (15.2)
Photosensitivity	20 (44.4)	19 (41.3)
Oral ulcers	16 (35.5)	9 (19.5)
Arthritis	31 (68.8)	27 (58.7)
Renal disorders	29 (64.4)	26 (56.5)
Neurologic disorders	8 (17.7)	5 (10.8)
Serositis	22 (48.8)	23 (50)
Hematologic disorders	27 (60)	20 (43.4)
Immunologic disorders	35 (77.7)	31 (67.4)
Antinuclear antibodies	44 (97.7)	45 (97.8)

aPL = antiphospholipid antibodies. * systemic disease activity assessed by the Systemic Lupus Activity Measure.

Normal values were determined by evaluating sera from 40 healthy subjects, free from any pathologic condition.

The cut-off of abnormal values for our laboratory was 6.33 for GPL and 6.21 for MPL. According to Harris standards[16-19] high levels of aPL are considered values of more than 8 times the cut-off; thus for our laboratory data, 8 times the cut-off of GPL equals 50.64, while MPL equals 49.68. For this reason we rounded off the Units for both GPL and MPL to 50 and arbitrarily identified those not exceeding 50 Units for both GPL and MPL as low level patients we considered those exceeding 50 Units as high level patients of at least one of the two above mentioned isotypes.

Echocardiographic examination. All 91 patients underwent an echocardiographic examination: 75 according to standard techniques, while 16 performed transesophageal echocardiography because of an inadequate transthoracic approach.

Cardiac abnormalities were considered: valvular regurgitation and/or stenosis (associated or not with Libman-Sacks vegetations), pericardial effusion, and regional myocardial wall dysfunction.

Mitral regurgitation was defined as meeting the following criteria[20]: length of mosaic color jet > 1 cm, color jet identified in at least two planes, and persistence of systolic turbolence during systole. We did not consider trivial regurgitation that is possible to observe at color Doppler also in healthy subjects and we adopted a semiquantitative assessment of valvular regurgitation, according to echocardiographic criteria, to distinguish mild from moderate-severe regurgitation: in particular, as mild regurgitation we identified a retrograde turbolence without enlargement of cardiac chambers.

We also evaluated myocardial hypertrophy presumably as a consequence of elevated blood pressure, due to renal involvement.

To evaluate wall motion, the left ventricle was divided into 11 segments: basal and mid portion of anterior, lateral, septal, posterior and inferior walls and finally apex. Regional wall motion abnormality was defined as contractility impairment of at least one ventricular segment, detected with the help of a computer-assisted continuous loop imaging of a single cardiac cycle. Contractility was evaluated independently by two experienced observers: in the case of disagreement, the final result was adjudicated by a subsequent joint review.

The χ^2 test was used for the statistical analysis of data. For smaller groups of samples the Fisher's exact test was employed.

Results

Echocardiographic findings. Systemic lupus erythematosus population. Overall, 26 patients were completely free from echocardiographic abnormalities and 12 showed aspecific alterations. We did not include mi-

nor valvular lesions apparently related to other conditions such as mitral prolapse relatively frequent in females[7], valve thickening which is not a rare finding at echocardiography even in the normal population and also affected by an interobserver variability, and, finally, annular calcification which is associated with aging.

Cardiac alterations, likely associated with underlying disease, were detected in 53 patients (13 of these showed more than one lesion).

Valvular disease was present in 39 cases: in the great majority the mitral valve was involved (in 18 as isolated mitral regurgitation and in 4 as mixed disease); masses or vegetations suggesting Libman-Sacks atypical endocarditis were observed in 9 cases.

Aortic valve disease was detected in 12 patients (10 of whom as isolated aortic regurgitation), tricuspid in 4 and pulmonary in only 1 case.

These lesions were classified as "mild" in 25 cases and "moderate" in 13 patients. Severe lesion was detected in only 1 female patient, aged 54; the aorta was tricuspid and there was no history of rheumatic disease or heart murmur prior to the diagnosis of SLE. The overall clinical condition was progressive and valvular incompetence worsened in a short time leading to severe regurgitation which required surgery.

Pericardial effusion was detected in 19 patients, 11 of whom of mild degree and 7 of moderate degree. In only 1 case a severe effusion, with the feature of cardiac tamponade during follow-up, required an acute pericardial paracentesis and early immunosuppressive treatment.

In all patients the overall left ventricular function was preserved with a calculated ejection fraction exceeding 55%.

Left ventricular hypertrophy secondary to high blood pressure, was present in 14 patients. All these results are summarized in table II.

Regional wall motion dysfunction was present in 8 patients (Table III), in 5 as single, while in 3 as multiple segmental hypokinesis: the anterior wall was involved in 4 cases, the septal in 4 cases, the apex in 2 and the inferior wall in 1 patient. Regional akinesis or dyskinesis was never observed.

Antiphospholipid antibodies. When we correlated the incidence of endocardial involvement with the presence of aPL, we found that valvular heart disease was present in 22 patients (48.8%) of Group 1 (14 of whom with high aPL levels and 8 with low levels) and in 17 patients (36.9%) of Group 2 (p = NS).

However, while "mild" degree valvular disease was equally distributed between the two groups (p = NS), a moderate degree was present in 10 patients of Group 1 (9 of whom of Group 1A) and in 3 of Group 2. In addition the only patient with severe aortic disease (who required valvular replacement) also belonged to Group 1A, as shown in table II (p = 0.02).

Pericardial effusion was evident in 8 patients (17.7%) of Group 1 and in 11 patients (23.9%) of Group 2. This difference did not reach any statistical significance. Finally, left ventricular hypertrophy was present in 6 pa-

Table II. Prevalence of antiphospholipid antibodies (aPL) in systemic lupus erythematosus patients with echocardiographic abnormalities.

Echocardiographic findings	No. patients	aPL positive			aPL negative	p
		Total	High levels	Low levels		
Pericardial disease	19	8	4	4	11	NS
Valvular involvement	39	22	14*	8	17	NS (< 0.05)**
Left ventricular dysfunction (segmental)	8	7	4	3	1	< 0.05
Left ventricular hypertrophy	14	6	4	2	8	NS

* Libman-Sacks and/or stenosis and/or regurgitation; ** correlation between high aPL level positive patients and aPL negative patients.

Table III. Clinical features of 8 systemic lupus erythematosus patients with echocardiographically detectable regional wall dysfunction.

Patient	Age (years)	Sex	aPL group	Smoke	Hypertension	Hyperlipemia	Diabetes	Renal failure	Wall kinesis abnormalities	Coronary angiography
1	44	F	2	No	Yes	Yes	No	Yes	Mid anterior, apex, mid septal	1 vessel disease
2	32	F	1A	Yes	No	No	No	No	Basal anterior	Normal
3	35	F	1B	No	No	No	No	No	Mid inferior	Not performed
4	41	F	1B	No	Yes	No	No	No	Apex	Not performed
5	46	F	1A	No	No	No	No	No	Mid septal	Normal
6	33	M	1A	Yes	Yes	No	No	No	Mid anterior, mid septal	Normal
7	28	F	1A	No	No	Yes	No	No	Basal and mid anterior	Not performed
8	25	F	1B	No	No	No	No	No	Mid septal	Normal

aPL = antiphospholipid antibodies.

tients of Group 1 and in 8 patients of Group 2 (p = NS).

Regional wall motion abnormalities were present in 7 patients of Group 1 (4 with high and 3 with low aPL levels) and only 1 of Group 2 (p = 0.03). It is noteworthy to underline that those patients of Group 1 were free from history and heart-related symptoms as well as relevant risk factors.

All these 8 patients showed perfusion abnormalities of variable degree at technetium-99 sestamibi SPECT.

Coronary angiography. Four Group 1 patients, who had shown regional hypokinesis, underwent cardiac catheterization and coronary angiography which demonstrated normal epicardial vessels. On the other hand, the coronary angiogram of the only patient in Group 2, with renal failure, hypertension and hyperlipidemia, showed a mild stenosis of the left main and a subocclusion of the first diagonal branch.

Discussion

The goal of this study was to evaluate the incidence of pericardial, valvular, and myocardial lesions, detected by echocardiography, in patients with SLE, and the possible relationship with increased aPL levels.

Pericardial effusion was detected in 20.8% of SLE patients, particularly in those with an active disease; however, pericardial tamponade was present only in 1 patient, and constrictive pericarditis has not been observed so far. Thus our data suggest that aPL do not appear to play a specific role in pericardial involvement, since no difference was found between the two groups.

Valvular heart disease was commonly detected in both groups of SLE patients and the incidence of endocardial disease appears to be higher in patients with associated aPL, although this difference does not always reach statistical significance.

We must also consider that patients with high aPL levels showed not only a higher incidence of valvular disease in comparison to those with low levels but, moreover, in patients of Group 1A the degree of valvular lesion was definitively more important if compared not only to Group 2, but also to Group 1B: only 1 patient underwent valvular replacement and showed high levels of autoantibodies. These data suggest that aPL play some role in the pathogenesis of the severity of valvular lesions. Therefore is not surprising that, in our series of SLE patients, a severe degree of damage occurred mostly in those with a higher titer of aPL. In patients with SLE, a wide spectrum of pathogenetic mechanisms underlying valve dysfunction should also be considered: they include acute valvular endothelium inflammation, necrotizing vasculitis with infiltration of valvular tissue, and/or nodular and mass calcification (possibly resulting from earlier episodes) and finally valvular fibrosis following corticosteroid therapy[21-25].

While previous studies regarding the relationship between the presence of aPL and valvular lesion have reported conflicting results, more recently there has been a consensus regarding this association[25,26]. When present in patients with SLE, aPL may increase the frequence and severity of the valvular damage through endothelial injury, activation of clotting factor, platelet deposition and thrombus formation.

Therefore aPL may be regarded as a heterogeneous group, including lupus anticoagulant, anticardiolipin antibodies, those directed against other phospholipids and finally those directed towards plasma protein such as B2-glicoprotein and prothrombin[27]. Thus, the difference in incidence and in the degree of valve lesions between patients with a low and high aPL titer may be explained by the fact that aPL act as a further aggressive antibody towards the endocardial surface, increasing the damage produced by SLE itself, as suggested by Vianna et al.[26].

Another interesting finding, in this study, is the incidence of wall motion abnormalities in patients with aPL suggesting a relation between the presence of aPL and regional ventricular dysfunction.

Even if coronary angiography was performed in a limited number of patients, in none of these SLE patients of Group 1 was any obstructive lesion of major epicardial vessels detected; thus a small-vessel disease supported by microvascular thrombosis might be considered in the pathogenesis of ventricular wall abnormalities.

This hypothesis appears to be supported by the perfusion alteration, as documented by MIBI myocardial SPECT, described in detail in a previous study[28].

As reported by Asherson[29] in 1992, in necropsy studies of patients who died because of the so-called "catastrophic syndrome", microinfarts were found supported by small intramyocardial artery diseases due to occlusive thrombi without evidence of vasculitis.

Conversely, the coronary artery disease documented only in 1 Group 2 patient was clearly due to "accelerated atherosclerosis" in the arteries damaged not only by vasculitis but also by concomitant hyperlipidemia and hypertension, possibly secondary to renal involvement and long-term steroid treatment. More recently this finding has been related to the presence of antibodies to oxidized LDL. Cross-reactivity between autoantibodies against cardiolipin and with aPL, probably because of their binding to oxidized phospholipids, has been shown in patients with SLE[30]. In vitro studies have pointed out that these antibodies to oxidized LDL may enhance lipid accumulation into macrophages of atherosclerotic plaque vessels leading to a progression of the disease[31]. Prospective studies have reported a frequent occurrence and association of these antibodies with arterial thrombosis in patients with SLE and antiphospholipid syndrome suggesting a role in the development of "accelerated atherosclerosis"[32].

The possible diagnosis of myocarditis as a cause of wall motion abnormalities has been considered but we

believe that in these cases echocardiography usually shows a left ventricular dysfunction and involvement of at least a whole ventricular wall[33]; in other cases of myocarditis it is possible to observe a non-homogeneous distribution of contractility impairment with some areas of hypokinesis, or akinesis/dyskinesis alternated to normally functioning segments. Patients enrolled in this study, showed no global ventricular dysfunction and only regional hypokinesis was detected. The number of regional segments shows a trend of correlation with aPL titer, as shown in table III, and the severity of valvular abnormalities is significantly correlated with the presence and titer of aPL. Unfortunately, the limited number of patients enrolled did not allow us to draw any definitive conclusion which should be confirmed by larger studies, with adequate statistical power.

Study limitations. First of all, we determined aPL using the cardiolipin as coated antigen (ELISA). Other authors suggest that aPL are directed against phospholipid-protein complexes, as part of a broader family of autoantibodies with immunologic specificity for various phospholipid binding plasma proteins involved in hemostatic reactions[34]. Thus with the ELISA test, currently used in clinical practice, we were not able to detect all these heterogeneous autoantibodies.

Finally, we must underline that the echocardiographic study was performed by the standard rest examination which cannot detect the real incidence of kinetic abnormalities, which are more evident during exercise. It is likewise to predict that if echocardiographic test could be done under stress condition, the number of patients with wall motion abnormalities would increase, mostly in the aPL group.

In conclusion, aPL are frequently present in patients with SLE: there is evidence that the presence of aPL, when associated with the typical clinical syndrome, is correlated with a worse prognosis in patients with SLE if compared to patients without aPL[35].

Thus, even though aPL cannot be considered a typical marker of the disease, if present, they may be considered a criterium of the severity of the disease, particularly for long-term prognosis.

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