An Echocardiographic Study of Valvular Heart Disease Associated with Systemic Lupus Erythematosus

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ABSTRACT:

BACKGROUND:

Valvular heart disease is the most important cardiac manifestation of systemic lupus erythematosus (SLE). We performed a study to determine the relation of valvular disease to other clinical features of lupus, the type and the incidence of valvular heart disease in SLE patients.

METHODS:

We performed transthoracic echocardiography (TTE) and rheumatologic evaluations in 56 patients with systemic lupus erythematosus. The echocardiographic findings were compared with those in 40 healthy volunteers.

RESULT:

Abnormal valvular Echocardiographic findings were multiple valvular abnormalities found in 21 patients (37.5%), were distributed in three groups according of valvular involvement: (Group1) included patients with anatomical and functional valvular involvement (AFVI) in seven patients (12.5%). (Group2) included patients with anatomical valvular involvement without Doppler detected valve dysfunction (AVI) in 11 patients (19.6%). (Group3) included patients with functional abnormalities (stenosis or regurgitation) without valvular thickening (FVI) in three patients (5.3%). Positive antiphospholipids antibody (aPLs) was found in a total of 29 patients (51.7%), of those 17 patients (58.6%) had valvular echocardiographic abnormalities and four patients (14.8%) of the 27 patients with negative aPLs had abnormal echocardiographic findings.

CONCLUSIONS:

Valvular heart disease is common in patients with SLE, valvular abnormalities were correlated with the aPLs in patients with SLE. Echocardiography is an excellent tool for the diagnosis and follows up of valvular abnormalities in patients with SLE.

KEY WARDS: Systemic lupus erythematosus; echocardiography; heart

INTRODUCTION:

SLE is an extra ordinary complex autoimmune disorder that touches nearly all medical subspecialties. Evidence from a broad range of basic science studies indicates that the pathogenesis of this disease is equally complex and may vary from a patient to patient. The diverse expression of the common lupus syndrome may results from variable abnormalities in intersecting genetic, immunologic, hormonal, and environmental pathways.[1,2] Cardiovascular involvement has been receiving increased attention in patients with SLE. Prospective studies using advanced diagnostic methods have allowed the delineation of the prevalence and significance of discrete cardiac manifestation such as valvular disease myocardial dysfunction and pericardial involvement.[3,4,5] In other studies coronary artery disease have seen found to have a substantial effect on mortality and morbidity in patients with SLE It accounts for as many as one third of deaths seen in this population. [6]

SLE is a vascular disorder of connective tissue, mediated by autoantibodies directed against cellular antigens that results in multisystemic inflammatory damage. Cardiac lesions involving the endocardium, myocardium. Myocardium and coronary vessels have been commonly found in autopsy studies.[8-10] Libman–Sacks endocarditis, also termed 'atypical verrucous endocarditis' Anatomical and functional valvular abnormalities have been described in SLE,

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is the most characteristic lesion.[11] However, valvular thickening and regurgitation are more frequently observed than verrucous endocarditis. Anatomical lesions were observed in 15–75% in autopsy studies,[12] in 40–50% of cases with the transthoracic echocardiography (TTE) and in 50–60% with transesophageal echocardiography (TEE).[13]

The relation between aPLs antibodies and the development of cardiac valvular lesions is controversial. Valvular lesions have been seen with increasing frequency in patients with the primary antiphospholipid syndrome and in patients with SLE and aPLs antibody, this has led to speculation about a possible causal relation However valvular abnormalities are also seen in patients with SLE who lack antiphospholipid antibodies, this suggests that additional pathogenetic factors may be operative in the development of endocardial lesions in patients With SLE. [14,15,16]

The aim of the present study was to analyze the prevalence of endocardial involvement in living population of patients with SLE by the means of echocardiography and to describe its morphologic types functional relevance.

METHODS:

The study began in 1997 with a prospective design. An appointment was scheduled to 56 patients whose SLE was diagnosed at the outpatient clinic of the internal medicine service at Alrasheed- Teaching Hospital/Baghdad. All were in clinical remission, none had a history suggestive of rheumatic fever or infective endocarditis, no patient was specifically referred because of suspected valvular involvement. There were 10 male and 46 female patients, with a mean age of 28.9 ±7.7 years (range. 16 to 46) and 40 healthy subjects, matched to the study population for age and sex (mean age. 25±9 years: range 15 to 44: 8 male and 32 female) were prospectively evaluated as a control group for this study All the patients included in the study met the revised diagnostic criteria of the American Rheumatism Association for the classification of systemic lupus.[17] Clinical activity was considered to be present at the time of the initial echocardiographic study if the patients had at least three of the following abnormalities: fever, with no apparent infective cause, serositis, recent skin lesions or exacerbation of old ones, recent onset or acceleration of alopecia, nasobuccal ulcerations, active central nervous system involvement, increasing lymphadenopathy, leucopenia, or thrombopenia, an erythrocyte sedimentation rate exceeding 50 mm per hour in the absence of infection hypocomplementemia and features of active nephritis. A thorough clinical history was obtained from all patients and all underwent a physical examination, standard 12-lead electrocardiography, and chest roentgenographv. Tilers of antinuclear and anti-DNA antibodies and complement were measured.

All patients underwent the prothrombin time (PT), partial thromboplastin time (PTT) and the kaolin clotting time (KCT) and correction studies (with normal plasma) if these are required, a KCT index was determined , which is based on doing KCT for a mixture of 80% of normal plasma plus 20% patients plasma and then dividing this on KCT of normal plasma and if this index > 1.2 then this confirms the presence of a lupus anticoagulant.

The reagent Cardiolipin Enzyme-Linked immunosorbant assay (ELISA) (Diagnostic Automation Co) (U.S.A.) was used for the detection and quantitative determination of total anti-cardiolipin anti- bodies in sera of the patients .

The patients included underwent M-mode and two dimensional Doppler echocardiography using an ATL

(Ultramark) MK 60 recorder with a 2.5 MHz transducer.

The patients were examined in the standard views supine and in the left lateral position by two separate observers experienced in echocardiography and they were unaware of the clinical state of the patients, global and nodular thickening of the valve leaflets were accurately defined and colour Doppler studies were done to assess the presence and severity of valvular dysfunction. Mitral regurgitation was defined as a holosystolic flow reversal into the left atrium. Tricuspid regurgitation was a holo systolic flow reversal into the right atrium, aortic regulation was defined as holo-diastolic flow reversal into the left ventricle, pulmonary was a holo-diastolic flow reversal into the right ventricle. Regurgitation was mild if it mapped < 2cm behind the affected valve, moderate if mapped 2-4 cm into the affected chamber and sever if it mapped > 4 cm behind the affected valve , pulmonary and Tricuspid regurgitation was not quantitated.

The presence of minimal regurgitation near the valvular plane was not considered as significant in

the absence organic valvular disease and auscultatory findings. In the event of disagreement, the two reviewers reached a consensus by a joint review of the study. Thickening of the Mitral valve leaflets were assessed with M- mode echocardiography and of the Tricuspid valve with two dimensional echocardiography with the four chamber view. The aortic valve was assessed by M- mode and two dimensional studies. A valvular vegetation was defined as an abnormal localized echodensity with well defined borders either part of or adjacent to valve leaflets. Echocardiographic findings was identified as following; Global mitral valve thickening (GMVT), Nodular mitral valve thickening (NMVT), Global aortic valve thickening (GAVT), Nodular aortic valve thickening (NAVT), Global tricuspid valve thickening (GTVT), mitral regurgitation (MR), aortic regurgitation (AR), tricuspid regurgitation (TR), and according to the presence of anatomical or functional valvular disorders we divide our patients in to three groups: (Group1) included patients with anatomical and functional valvular involvement (AFVI), (Group2) included patients with anatomical valvular involvement without Doppler detected valve dysfunction (AVI), (Group3) included patients with functional abnormalities (stenosis or regurgitation) without valvular thickening (FVI).

Forty control subjects were examined in the same manner, they were Free of infection and they have no history of heart problem or of chronic drug intake.

The statistical significance of difference in mean of a continuous outcome variable which is known or assumed to be normally distributed between two groups was measured by t-test. The statistical significance of association between two categorical variables was measured by Chi - square test or by exact tests when the criteria for valid Chi-square test were not met. An estimate was considered statistically significant if its value was less than 0.05.

RESULTS:

Clinical

The age of the 56 patients included ranged between 16 - 46 years with a mean of (28.9± 7.7) years. Forty six patients were females and ten males. The duration of the illness ranged between five months and 21 years with a mean of (6.5± 5) years. The duration of steroid and / or immunosuppressive treatment between three months and 16 years with a mean of (4.1±3.5) years, three patients were not receiving steroids. The most frequently encountered finding was arthralgia (91.07%) (which involved one or more joints- mostly multiple), followed by skin and mucous membrane manifestations including malar rash (83.9%), discoid rash (25%), and oral ulcers (50%). Neuropsychiatric findings were also commonly found in (44.6%) in our patients and included cerebrovascular accidents (CVA), transient ischemic attaches TIAs, unilateral blindness, seizures, migraine, psychosis and depression. Renal impairment as defined by a serum creatinine level above 1.5 mg/ dl was present in 18 patients (32.1%), while abnormal renal deposits defined by the presence of proteinuria of more than 500 mg/24 hour, the presence of casts (including red cells, granular, and tubular or mixed) the presence of hematuria (> 5 RBC / HPF) in the absence of infection was found in 16 patients (28.5%). Recurrent fetal loss as defined by three or more consecutive fetal losses either as first trimester miscarriage or later fetal loss with evidence of growth retardation or without was found in 12 patients (30%) of married females. Recurrent deep vein thrombosis (DVT) were found in 13 patients (23.02%) and it was diagnosed clinically and by ultrasonic Doppler studies or venography reports for previous thrombosis, in addition to DVT other thrombotic events included CVA two patients, ischemic heart disease in three patients, Budd-Chiari syndrome one patient, pulmonary embolism (1 patient), TIAs in seven patients and retinal vein thrombosis two patients so that the total number of patients with thrombotic events was 29 (51.7%) (Table1). Anticardiolipin antibodies (aCL) were detected in 21 patients (37.5%) including three patients (5.3%) had both aCL and Lupus anticoagulant (LA) and eight patients (14.2%) had only the LA , thus antiphospholipids antibodies (LA and / or aCL) were found in a total of 29 patients (51.7%).

Echocardiographic and dopplar study

On the basis of the echocardiographic study patients were classified into three groups:-

Group one included patients with anatomical and functional valvular involvement (AFVI) in seven patients (12.5%) showed a valvular involvement classified as AFVI, in all patients the mitral valve was involved; five of them the valve was globally thickened and the other two showed nodular thickening (Libman-Sacks vegetations). The

abnormality included both leaflets and has no predilection to a specific site. Global aortic valve thickening was associated in two patients and global bicuspid valve thickening in one patient, doppler detected moderately sever MR in five patients (in one of them there was an associated TR), mild MR in one patient and mixed mild MR and AR in another one.

Group two

included patients with anatomical valvular involvement without doppler detected valve dysfunction (AVI) in 11 patients (19.6%) showed a valvular involvement classified as AVI. In all patients the mitral valve was involved; seven with global valve thickening and four with nodular thickening of the valve leaflets (Libman-Sacks vegetations). Aortic valve thickening was associated in three patients; two patients with global thickening and one patient with nodular thickening the abnormalities were only anatomical and there was no doppler detected abnormalities.

Group three: -

included patients with functional abnormalities (stenosis or regurgitation) without valvular thickening (FVI) in three patients (5.3%) were classified as FVI. doppler detected moderately sever MR in two patients and moderate AR in one patient.

As we see from the above finding abnormal valvular echocardiographic findings were found 36 valvular lesions in 21 patients (37.5%); (10 patients with single valvular lesion and 11 with more than one valvular lesion). Global valvular thickening was the most frequent finding in 14 patients (25%); (9 mitral valve, two aortic, two mixed, and one mitral with tricuspid). While nodular valve with variable size vegetations (Libman-Sacks vegetations) in six (10.7%); (five mitral, one mitral and aortic), MR in nine (16.07%), AR in two (3.5%), and TR in one (1.7%). No abnormalities were detected on the pulmonary valve. (Table 2) shows some clinical parameters in SLE patients with details abnormal echocardiographic finding.

Echocardiographic findings in the control group

M-mode, two dimensional and color Doppler echocardiographic studies were performed in forty healthy age and sex matched persons, two persons showed short localized echogenic mass at the anterior mitral valve leaflet tip associated with a regurgitant jet on color doppler immediately behind the valve both patients were above the age of forty.

Another two patients showed systolic prolapse of the posterior leaflet without thickening of the valve so they were not regarded as being abnormal (in our patients we excluded patients with MVP without thickening of the valves).

When compared to the control group our patients had significantly more incidence of echocardiographic abnormalities ($p<0.05$) (Table 3).

Our patients had also a significantly higher incidence of anticardiolipin antibodies in their sera when compared to the control group ($p<0.05$) (Table 4). Of the 21 patients with abnormal valvular echocardiographic findings, 17 patients (80.9%) showed a positive test for aPLs and it was statistically significant ($p<0.05$) (Table4).

Our study found no association between the duration of SLE disease with the incidence of valvular abnormalities when compared to patients with SLE and no valvular abnormality (Table 5).

The present study found no association between the duration of steroid treatment with the incidence of valvular abnormalities (Table 6).

DISCUSSION:

SLE can affect most parts of the cardiovascular system, and several autopsy series have shown a high incidence of pericardial (53-74%), endocardial (48-50%), and myocardial involvement.[18-20] These data do not necessarily reflect the prevalence of cardiovascular involvement in the living population. Echocardiography provides a readily available noninvasive technique that can be used to identify the spectrum of cardiac abnormalities. The introduction of echocardiographic diagnostic techniques however, revealed a frequent occurrence of globally thickened functionally impaired cardiac valves that were prone to hemodynamic deterioration in SLE patients.[21-23] It has been postulated that the two morphologic types of valvular lesions represent different stages of the same pathological process. The shift in valve pathology has been ascribed to steroid therapy and generally longer survival of patients with SLE, presumably allowing the more frequent emergence of fibrosed malfunctioning valves as the end stage or healed form of Libman Sacks endocarditis. [22,24-26]

In line with previous reports, we have identified a wide spectrum of valvular lesions, ranging from global valve thickening to nodular thickening with or Without valve dysfunction was found in 21 patients (37.5%) Libman-Sacks endocarditis in six patients (10.7%), global thickening of the valve leaflets in 14

patients (25%), MR in nine patients (16%), AR in two patients (3.5%), and TR in one patient (1.7%).
Leung et al [27] in 1990 reported an overall incidence of valvular abnormalities to be 34% in 75 patients with SLE, nine patients (12%) with Libman-Sacks endocarditis, six patients (8%) with global thickening, MR in 25% of patients, AR in 8% of patients, TR in 5% , and PR in1%.
Galve et al [21] reported 18% of valvular abnormalities in 74 patients with SLE, seven patients (9%) with Libman-Sacks endocarditis, six patients (8%) with globally thickened valve and 20% with MR. Nihoyannopoulos et al [14] reported 28% overall incidence of valvular abnormalities with 9% incidence of Libman-Sacks endocarditis and 20% incidence of global valve thickening in 93 patients with SLE.
Giunta et al [28] reported 37% overall incidence of valvular abnormalities, 8% with nodular thickening of the valve and 15% incidence of global thickening.
The overall incidence of valvular abnormalities in our study was comparable to that reported by Giunta et al and Leung et al and higher than others. The incidence of Libman-Sacks endocarditis in our study was slightly lower than that reported by Leung et al and slightly higher than that reported by Giunta et al, Nihoyannopoulos et al, and Galve et al, (Table7).
Like in other studies the mitral valve was the commonest to be involved followed by the aortic and then the tricuspid.
Carlos A et al [29] in 1996 using TEE reported valvular abnormalities in 61% in 69 patients with SLE, global valve thickening was the predominant finding (51%), followed by valve vegetations 43%, MR in 25%, AR in 6%, and TR in 3%. The sequence of involvement was comparable to our study but the incidence is lower because the resolution of the TEE is much higher than the TTE used in our study.
Of the 21 patients with SLE and valvular abnormalities, 17 patients (80.9%) showed a positive test for aPLs, 72.4% of aPLs positive patients showed valvular abnormality and 14.8% of aPLs negative patients had valvular abnormalities ($p<0.05$) and it was statistically significant.
Our results were similar to that reported by Khamashta et al [30] who reported 28% incidence of valvular abnormalities, 46% of aPLs positive patients (23 out of 50) had valvular abnormalities, and 10.9% of aPLs negative patients had valvular abnormalities (nine out of 82) and it was statistically significant ($p<0.001$). Similarly Nihoyannopoulos et al [14] reported 40% of aPLs positive patients (20 out of 50) and 13.9% of aPLs negative patients (six out of 43) had valvular abnormalities ($p<0.05$) and it was statistically significant.
The differences between studies in the prevalence of valvular defects observed among SLE patients and their association with aPLs could be due in part to different methods of aPLs detection, variances in echocardiographic techniques and interpretation of results.
In our study we did not find significant association between the duration of the disease and the duration of steroid treatment with the incidence of valvular abnormalities, 11 patients (52.2%) were receiving steroid for more than five years with echocardiographic valvular abnormalities and 19 patients (54.2%) were receiving steroids for more than five years without echocardiographic valvular abnormalities ($p>0.05$). Seventeen patients (80.9%) with valvular abnormalities had a duration of the disease of more than one year and 33 patients (94.2%) without valvular abnormalities had a duration of the disease more than one year ($p>0.05$). our results were similar to other series, who concluded that clinically significant SLE valvular heart disease is not necessarily the result of long standing disease [3,5,30,32,33].
In Conclusion the heart valves are a common targets in SLE and special attention should be offered for examination and follow up for their involvement. TTE is an excellent tool for the diagnosis and follow up of valvular abnormalities in patients with SLE. The mitral valve is the commonest to be involved with global valve thickening and mitral regurgitation being the predominant findings. Nodular thickening of the valves (Libman-Sacks endocarditis) is the next predominant finding. Involvement of the aortic and tricuspid valves was less common. Valve dysfunction in the form of regurgitation is exceedingly more common than stenosis. Like other thrombotic phenomenon, valvular abnormalities were correlated with the antiphospholipid antibodies in patients with SLE. Valvular abnormalities are not necessarily the result of long standing disease or long standing steroid treatment.

Table.1 Clinical parameters in 56 Iraqi patients with SLE included in this study

Clinical parameters	Number	%
Malar rash	51	91.07
Discoid rash	14	25
Photosensitivity	40	71.4
Oral ulcers	28	50
Arthralgia and arthritis	51	91.07
Serositis	12	21.4
Renal disorder	32	57.1
Neurologic disorder	25	44.6
Hematologic disorder	34	60.7
ANA	48	85.7
DVT	13	23.2
Pulmonary embolism	1	1.7
IHD	2	5.3
Recurrent fetal loss	12	33.3*

* this percentage refers for married female

Table 2 Clinical data of 21 patients with valvular echocardiographic abnormalities (except mitral valve prolapse)

Patients	Sex Age	Disease duration	Echo finding	aPL,LA and/ oraCL	comments
1	F 26	9 months	GMVT , MR	aCL	—
2	F 45	11 years	GMVT , MR	— ve	—
3	F 32	3years	GMVT,MR	LA	RFL
4	F 41	14 years	GMVT,MR	aCL , LA	RFL , DVf ,TIA , Fits
5	F 40	18 years	GMVT , GTVT , MR,TR	LA	Migraine , TIA
6	F 16	3 years	NMVT,GAVT	aCL	Fits
7	M 23	5 years	NMVT, GAVT, MR ,AR	aCL , LA	Thrombocytopenia DVT
8	M 40	8 years	GMVT, MR	— ve	Angina
9	F 28	3 years	GMVT	aCL	DVT , TIA
10	F 34	21 years	GMVT	aCL	—
11	F 24	2 years	GMVT	aCL	—
12	F 45	12 years	GMVT	— ve	—
13	F 35	8 years	GMVT,GAVT	LA	Vasculitis , DVT
14	F 39	2 years	GMVT,GAVT	aCL	RFL preclampsia
15	F 41	8 years	NMVT,NAVT	aCL	RFL,DVT
16	F 26	18 years	NMVT	aCL	—
17	M 28	8 years	NMVT	aCL	—
18	F 24	5 years	NMVT	aCL	DVT", Migraine Thrombocytopena
19	F 33	1 years	MR	LA	—
20	M 26	18 years	MR	- ve	—
21	F 26	5 months	AR	aCL	DVT , LR |

(GMVT): Global mitral valve thickenin. (NMVT): Nodular mitral valve thickening. (GAVT): Global aortic valve thickening. (NAVT): Nodular aortic valve thickening (GTVT):Global tricuspid valvethickening (LR): Livedo reticularis.
(RFL) : Recurrent fetal loss , (TIA) : Transient ischemic attack .

Table 3. Relation between echocariographic valvular abnormalities in patients with SLE and the control group statistically significant (P<0.05)

No. of Patients	patients with valvular abnormalities	patients without valvular abnormalities
Control (40)	4 (10%)	36 (90%)
SLE (56)	21 (37.5%)	35 (62.5%)

Table 4. relation between echocardiographic abnormalities in patients with SLE and aPls statistically significant difference (P<0.05)

aPLs	No.of patients with Valvular abnormalities 21 patients	No.of patients without Valvular abnormalities 35 patients
Positive 29 patients	17 (80.9%)	12 (34.2%)
Negative 27 patients	4 (19%)	23 (65.7%)
Total	21	35

Table 5. relation between echocardiographic valvular abnormalities and theduration of SLE(P > 0.05)

Duration of SLE	Patients with valvular abnormalities	Patients without valvular abnormalities
< 1 year	2	2
1-5 years	8	14
> 5 years	11	19
Total 56	21	35

Table 6. relation between echocardiographic valvular abnormalitiesand the duration of steroid treatment in SLE patients statistically not significant (P > 0.05)

Duration of steroid treatment	Patients with valvular abnormalities	Patients without valvular abnormalities
< 1 year	4	2
1-5 years	6	14
> 5 years	11	19
Total 56	21	35

Table 7. Frequencies of valvular involvement In patients with SLE in different studies

Study	Overall incidence	Global thickening	Nodular thickening	MR	AR
Leung et al [27]	34%	8%	12%	25%	8%
Calve et al [21]	18%	8%	7%	20%	6%
Nihoyannopoulos et al [14]	28%	20%	9%	—	—
Giunta et al [28]	37%	15%	8%		—
Present study	37.5%	25%	10.7%	16%	3.5%

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