

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. We performed a study to determine the relation of valvular disease to other clinical features of lupus, whether or not the valve disease progresses, and the associated morbidity and mortality.

Methods We performed transesophageal echocardiography and rheumatologic evaluations in 69 patients with systemic lupus erythematosus. The echocardiographic findings were compared with those in 56 healthy volunteers. Fifty-eight patients (84 percent) had second evaluations a mean (\pm SD) period of 29 ± 13 months later. The patients and controls were followed for 57 months.

Results Valvular abnormalities were common on the initial and the follow-up echocardiograms (in 61 and 53 percent of the patients, respectively). Valvular thickening was the predominant finding initially and on follow-up (in 51 and 52 percent of the patients, respectively), followed by vegetations (in 43 and 34 percent), valvular regurgitation (in 25 and 28 percent), and stenosis (in 4 and 3 percent). Valvular abnormalities frequently resolved, appeared for the first time, or persisted but changed in appearance or size between the two studies. Mild or moderate valvular regurgitation did not progress to become severe, and new stenoses did not develop. Neither the presence of valvular disease nor changes in the echocardiographic findings were temporally related to the duration, activity, or severity of lupus or to its treatment. The combined incidence of stroke, peripheral embolism, heart failure, infective endocarditis, and the need for valve replacement was 22 percent in the patients with valvular disease, but only 8 percent in those without it. A total of seven patients died during follow-up, in most cases as a result of valvular disease. Valvular abnormalities and complications were uncommon in the controls (occurring in 9 and 2 percent, respectively).

Conclusions Valvular heart disease is common in patients with systemic lupus erythematosus, frequently changes over time, appears to be temporally unrelated to other clinical features of lupus, and is associated with substantial morbidity and mortality. (N Engl J Med 1996;335:1424-30.)

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VALVULAR disease is the most prevalent and clinically important form of cardiac involvement in patients with systemic lupus erythematosus,¹⁻⁴ but little is known about its relation to the clinical features of the disorder. In addition, changes over time in valvular abnormalities and the incidence of severe valvular dysfunction, infective endocarditis, the need for valve replacement, cardioembolism, and death have not been evaluated.¹⁻⁷ We conducted a study to determine whether there is an association between the clinical features of lupus and valvular involvement, to assess changes over time in valvular abnormalities detected by serial transesophageal echocardiography, and to determine the incidence of complications associated with valvular disease during long-term follow-up.

METHODS

Study Population

From 1989 to 1996, we performed transesophageal echocardiography and rheumatologic evaluations in 69 patients with systemic lupus erythematosus. The initial echocardiographic findings in 54 of these patients have been reported elsewhere.⁴ The 69 patients represented 86 percent of the outpatients 60 years of age or younger who are followed by rheumatologists at our affiliated hospitals. Patients over 60 years old were excluded because of the high prevalence of degenerative valvular disease in this age group.⁸ Patients with a history of rheumatic fever or intravenous drug abuse were also excluded.

There were 61 women and 8 men in the study, with a mean age of 38 years (range, 16 to 57). A total of 58 patients (84 percent) underwent a repeated evaluation a mean (\pm SD) of 29 ± 13 months (range, 6 to 54) after the initial evaluation. Forty-two of the 58 were patients with stable lupus who underwent both evaluations as outpatients, with the second evaluation performed at least 12 months after the first. Sixteen patients had at least one hospital admission during the study period due to flares of the lupus or complications potentially related to valvular disease. The second evaluation was performed during hospitalization in 7 of the 16 patients, and within one month after discharge in 7. Initial echocardiographic findings were compared with those in 56 age-matched healthy volunteers (31 women and 25 men) with a mean age of 35 years (range, 17 to 54). The study was approved by the Human Research Committee at our institution, and all subjects provided informed consent.

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Echocardiographic Studies

All subjects underwent initial and follow-up transesophageal echocardiography with a color Doppler imaging system (Hewlett-Packard Sonos 500, 1500, or 2500). All echocardiograms were coded according to the patient's or control's Social Security number, and the studies in patients with lupus were interpreted in random order along with those in healthy volunteers. The echocardiograms were interpreted by an observer who was unaware of the clinical data and the timing of the studies. In addition to standard echocardiographic views,⁹ images of the heart valves were obtained at high magnification in multiple planes.

Electronic calipers were used to determine the thickness of the mitral, tricuspid, and aortic valves on transesophageal echocardiography in the patients and controls. The basal, middle, and tip portions of the atrioventricular-valve leaflets were measured with M-mode echocardiography (for the mitral valve) and two-dimensional echocardiography (for the tricuspid valve) in the four-chamber view. The midportion of the right and noncoronary cusps of the aortic valve was measured by M-mode echocardiography from the basilar short-axis and longitudinal views. The left coronary cusp was measured by two-dimensional echocardiography from the basilar short-axis view. In the normal subjects, the thickness of the mitral and tricuspid valves was 0.7 to 3 mm, and the aortic-valve thickness was 0.7 to 2 mm. Abnormal valvular thickening was therefore considered to be present when a thickness of more than 3 mm (for the mitral and tricuspid valves) or more than 2 mm (for the aortic valve) was observed in at least two leaflets or in one leaflet with an associated vegetation, at least mild regurgitation, or both. The pulmonic valve was not measured, because thickening of this valve was rare.

A valvular vegetation was defined as an abnormal localized echodensity with well-defined borders either part of or adjacent to valve leaflets, the subvalvular apparatus, or the great vessels. The size of the vegetation was determined by planimetry and expressed in square centimeters.

Mitral- or tricuspid-valve regurgitation was graded with the use of the color Doppler jet-area method.¹⁰ Aortic regurgitation was graded according to the ratio of the width of the color jet to the diameter of the outflow tract.¹¹ This method was derived from transthoracic studies and applied to transesophageal echocardiography. Pulmonic regurgitation was assessed visually. Regurgitation was considered to be present if it was more than mild or if it was mild and associated with valvular thickening or a vegetation of the respective valve. Minimal or mild regurgitation of a structurally normal valve was not documented.

The severity of valvular stenosis was assessed by calculating the valvular area, with the use of the continuity equation.¹²

Clinical Evaluation

All patients underwent a complete clinical evaluation at the time of each echocardiographic study. The activity of the lupus was assessed with the Lupus Activity Criteria Count.¹³ The disease was considered to be active if at least two of seven clinical and laboratory criteria were met. The severity of the disease was graded with the Lupus Severity of Disease Index¹⁴ and scored on a scale from 1 to 13.

A laboratory-activity score of 1 to 10 was derived from 10 laboratory abnormalities: a positive test for antinuclear antibodies (dilution, >1:40), a positive test for DNA antibodies (dilution, >1:10), anemia (<12 g of hemoglobin per deciliter), leukopenia (<4000 white cells per cubic millimeter), thrombocytopenia (<150,000 platelets per cubic millimeter), renal failure (>1.4 mg of creatinine per deciliter [$>120 \mu\text{mol}$ per liter]), hematuria (>5 red cells per high-power field), a low C3 value (<85 mg per deciliter), a low C4 value (<12 mg per deciliter), and a high erythrocyte sedimentation rate (>20 mm per hour).

The average dose of each drug taken during the three months preceding each echocardiographic study was assessed by chart reviews or personal or telephone interviews with the patients.

Morbidity and Mortality

Patients and controls were followed for 57 ± 12 and 57 ± 15 months, respectively. The incidences of stroke or peripheral embolism, heart failure, infective endocarditis, need for valve replacement, and death were determined by interviews with the patients and chart reviews.

Statistical Analysis

The frequency of and degree of change in valvular abnormalities in the patients and controls were compared with Fisher's exact test.¹⁵ Paired comparisons for binary variables were performed with McNemar's test.¹⁵ Student's and paired t-tests were used for the comparison of continuous variables.¹⁶ To assess interrater agreement in the detection of valvular abnormalities, a second independent observer interpreted 45 randomly selected echocardiograms from patients and controls. Interrater agreement was determined by the percentage of agreement between the two sets of readings, as well as by Cohen's kappa test.¹⁷ A two-tailed P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Valvular Abnormalities

In the patients with lupus, valvular abnormalities — predominantly of the mitral and aortic valves — were common on the initial echocardiogram (in 61 percent of the patients) and on the follow-up echocardiogram (in 53 percent). Abnormalities were

TABLE 1. FREQUENCY OF VALVULAR ABNORMALITIES ON TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND CONTROLS.

VALVULAR ABNORMALITY	INITIAL ECHOCARDIOGRAM		FOLLOW-UP ECHOCARDIOGRAM
	PATIENTS (N = 69)	CONTROLS (N = 56)	PATIENTS (N = 58)
no. of subjects (%)			
Thickening	35 (51)	4 (7)*	30 (52)†
Mitral	26 (38)	1 (2)	23 (40)
Aortic	21 (30)	2 (4)	15 (26)
Tricuspid	3 (4)	0	1 (2)
Pulmonic	0	1 (2)	0
Vegetations	30 (43)	0*	20 (34)†
Mitral	22 (32)	0	16 (28)
Aortic	13 (19)	0	8 (14)
Tricuspid	2 (3)	0	1 (2)
Pulmonic	1 (1)	0	0
Regurgitation	17 (25)	1 (2)*	16 (28)
Mitral	13 (19)	0	13 (22)
Aortic	4 (6)	1 (2)	4 (7)
Tricuspid	2 (3)	0	1 (2)
Stenosis	3 (4)	1 (2)	2 (3)
Any abnormality	42 (61)	5 (9)*‡	31 (53)

* $P < 0.001$ for the comparison between the patients and the controls. There were no significant differences between the initial and follow-up echocardiographic studies in the patients.

†Among the patients, $P < 0.01$ for the comparison between valvular thickening or vegetations and regurgitation on the initial echocardiogram and $P < 0.01$ for the comparison between valvular thickening and vegetations or regurgitation on the follow-up echocardiogram.

‡Two controls had mitral-valve prolapse, one had mild pulmonic-valve stenosis, one had a mildly regurgitant bicuspid aortic valve, and one had aortic-valve sclerosis.

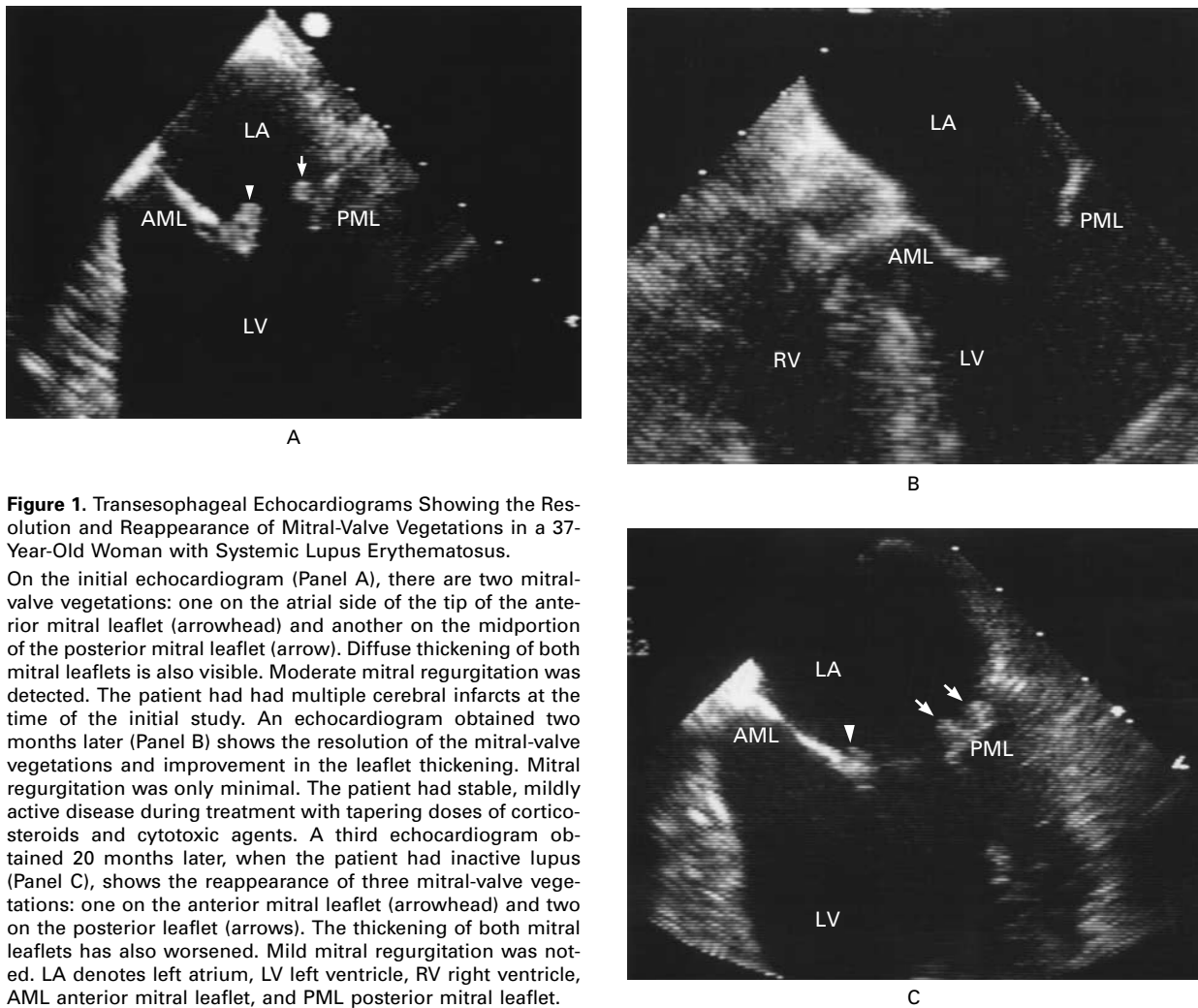


Figure 1. Transesophageal Echocardiograms Showing the Resolution and Reappearance of Mitral-Valve Vegetations in a 37-Year-Old Woman with Systemic Lupus Erythematosus.

On the initial echocardiogram (Panel A), there are two mitral-valve vegetations: one on the atrial side of the tip of the anterior mitral leaflet (arrowhead) and another on the midportion of the posterior mitral leaflet (arrow). Diffuse thickening of both mitral leaflets is also visible. Moderate mitral regurgitation was detected. The patient had had multiple cerebral infarcts at the time of the initial study. An echocardiogram obtained two months later (Panel B) shows the resolution of the mitral-valve vegetations and improvement in the leaflet thickening. Mitral regurgitation was only minimal. The patient had stable, mildly active disease during treatment with tapering doses of corticosteroids and cytotoxic agents. A third echocardiogram obtained 20 months later, when the patient had inactive lupus (Panel C), shows the reappearance of three mitral-valve vegetations: one on the anterior mitral leaflet (arrowhead) and two on the posterior leaflet (arrows). The thickening of both mitral leaflets has also worsened. Mild mitral regurgitation was noted. LA denotes left atrium, LV left ventricle, RV right ventricle, AML anterior mitral leaflet, and PML posterior mitral leaflet.

present in only 9 percent of the controls ($P < 0.001$ for the comparison with the patients, for each abnormality except valvular stenosis) (Table 1).

Valvular thickening was the most common abnormality, and it was seen in approximately half the patients at each echocardiographic study. Valvular thickening was equally frequent on the mitral and aortic valves and was usually diffuse. Leaflet thickening was associated with decreased mobility in two thirds of the patients. Less than 10 percent of the patients had leaflet calcification or involvement of the annulus and subvalvular apparatus.

Valvular vegetations were present in 30 of the 69 patients (43 percent) initially and in 20 of 58 (34 percent) at follow-up. The vegetations were located on the basal, middle, or tip portions of the leaflets and were located predominantly on the atrial side of the mitral valve or on the vessel side of the aortic valve. Vegetations were of variable size (range, 0.06

to 1.25 cm²) and shape, had irregular borders, and frequently had heterogeneous echogenicity (Fig. 1). Two thirds of the patients with valvular vegetations had associated valvular thickening.

Valvular regurgitation was detected in about 25 percent of the patients at each echocardiographic study. The regurgitation was moderate or severe in 11 of 17 patients initially and in 8 of 16 at follow-up. Valvular stenoses were present in 4 percent of the patients initially and in 3 percent at follow-up.

Over half of the 45 echocardiograms evaluated by a second reader showed evidence of valvular disease. Overall, there was 96 percent agreement ($\kappa = 0.91$) between the two sets of readings. Agreement in detecting valvular vegetations was 98 percent for the aortic valve and 96 percent for the mitral valve. Similar results were obtained for valvular regurgitation (93 and 98 percent, respectively) and thickening (87 and 93 percent, respectively).

Nonvalvular Cardiac Diseases

Fifteen of the 69 patients (22 percent) had nonvalvular cardiac abnormalities. Four patients had segmental left ventricular dysfunction due to coronary artery disease, and five had global hypokinesis of unknown cause. Five patients had pericardial effusions, and one of the five had fatal cardiac tamponade. One patient had severe cor pulmonale due to recurrent pulmonary embolism.

Relation of Valvular Disease to Clinical Features of Lupus

The presence of valvular disease was not temporally related to the clinical features of lupus. The patient's age, the duration of the lupus, clinical or laboratory evidence of its activity and severity, and the duration or type of therapy did not differ according to the presence or absence of valvular abnormalities (Table 2).

Changes in Valvular Disease

Valvular abnormalities, especially vegetations, frequently resolved, appeared for the first time, or persisted but with changes in appearance or size during the period between the initial and follow-up echocardiograms (Table 3). In 14 patients (24 percent), 25 vegetations resolved, and in 7 patients (12 percent), 8 new vegetations were present at follow-up (Fig. 1). Thirteen patients (22 percent) had 19 vegetations initially but 27 at follow-up. In 8 of these 13 patients, some vegetations resolved, some appeared for the first time at follow-up, and some persisted but with changes in size or appearance between the initial and follow-up echocardiographic studies.

Only two patients who had mild regurgitation initially had moderate regurgitation at follow-up, and none had severe regurgitation. Only one patient with severe regurgitation at base line became symptomatic in the absence of coronary artery disease or infective endocarditis. No patients had new valvular stenoses at follow-up.

The clinical manifestations of lupus did not change between the two evaluations and did not differ according to whether valvular abnormalities resolved, appeared for the first time, or persisted at follow-up (Table 2).

Morbidity and Mortality

During almost five years of follow-up, 29 complications developed in 12 of 58 patients (21 percent), including 7 deaths (12 percent) (Table 4). Of the 10 patients with valvular disease and complications, 5 had 6 ischemic strokes and 1 peripheral embolism. Of these five patients (three of whom had valvular vegetations and two of whom had valvular thickening with regurgitation), three had multiple cerebral infarcts on magnetic resonance imaging at

TABLE 2. CLINICAL CHARACTERISTICS OF THE PATIENTS ACCORDING TO THE PRESENCE OR ABSENCE OF VALVULAR DISEASE.*

CHARACTERISTIC	INITIAL ECHOCARDIOGRAM		FOLLOW-UP ECHOCARDIOGRAM	
	VALVULAR DISEASE (N = 42)	NO VALVULAR DISEASE (N = 27)	VALVULAR DISEASE (N = 31)	NO VALVULAR DISEASE (N = 27)
Duration of SLE (yr)	9±7	8±7		
SLE severity index	4±2.5	3.6±2	4.7±2.8	4.6±2.7
Active SLE (% of patients)	66	73	52	70
SLE activity score	2.6±1.4	2.2±1.1	2±1.2	2.3±1.1
SLE laboratory score	3.5±1.8	2.7±2.4	3±2	2.4±2.3
Positive ANA test (% of patients)	92	92	97	84
ANA titer (dilutions)	339±246	358±274	428±252	320±280
C3 (mg/dl)	102±35	104±47	113±41	111±48
C4 (mg/dl)	21±13	23±13	23±10	23±18
Erythrocyte sedimentation rate (mm/hr)	35±28	30±28	56±30†	26±35
Positive DNA test (% of patients)	15	30	17	25
Medications				
Corticosteroids (% of patients)	52	58	38	54
Corticosteroid dose (mg/day)	27±22‡	13±9	15±11	18±11
Cytotoxic agents (% of patients)§	19	15	14	33
NSAIDs (% of patients)	38	46	45	38
Antimalarial agents (% of patients)	40	27	34	25
Anticoagulant agents (% of patients)	15	8	7	9

*Plus-minus values are means ±SD. SLE denotes systemic lupus erythematosus, ANA antinuclear antibody, and NSAIDs nonsteroidal antiinflammatory drugs.

†The severity, activity, and laboratory scores are explained in the Methods section.

‡P=0.01 for the comparison with the patients without valvular disease.

§The proportion of patients receiving cyclophosphamide or azathioprine and the doses of these drugs did not differ according to the presence or absence of valvular disease.

the time of the complications (Fig. 1). A sixth patient had a fatal hemorrhagic stroke while receiving anticoagulant therapy for a prosthetic valve. Five of the six patients with heart failure had severe valvular regurgitation, complicated by coronary artery disease in two and by infective endocarditis in two. Two of the patients underwent successful valve replacement, two declined surgery (both died from refractory heart failure), and one died from sepsis. In the sixth patient, right heart failure developed as a result of recurrent pulmonary embolism. Three patients had infective endocarditis of the mitral valve. In one of these patients, pathological studies con-

TABLE 3. CHANGES IN VALVULAR ABNORMALITIES BETWEEN INITIAL AND FOLLOW-UP TRANSESOPHAGEAL ECHOCARDIOGRAPHY.*

VALVULAR ABNORMALITY	CHANGES IN VALVULAR ABNORMALITY		
	RESOLVED	APPEARED	PERSISTED
	no. of patients (%)		
Thickening	10 (17)	7 (12)	23 (40)
Vegetations	14 (24)	7 (12)	13 (22)
Regurgitation	6 (10)	6 (10)	10 (17)

*Of the 58 patients who underwent follow-up echocardiography, 45 (78 percent) had abnormalities on at least one echocardiogram, and 13 (22 percent) did not have abnormalities on either echocardiogram.

TABLE 4. INCIDENCE OF COMPLICATIONS ACCORDING TO THE PRESENCE OR ABSENCE OF VALVULAR DISEASE.*

COMPLICATION	VALVULAR DISEASE (N = 45)†	No VALVULAR DISEASE (N = 13)
	no. of patients (%)	
Stroke or peripheral embolism	6 (13)‡	1 (8)
Heart failure	6 (13)	0
Infective endocarditis	3 (7)	0
Indication for valve replacement	4 (9)	0
Death	5 (11)	2 (15)
Any complication	10 (22)	2 (15)

*Only 1 of the 56 controls had a complication. For the comparisons between patients and controls, $P=0.06$ for stroke or peripheral embolism, $P=0.03$ for heart failure, $P=0.24$ for infective endocarditis, $P=0.004$ for valve replacement, $P=0.12$ for death, and $P=0.03$ for any complication.

†All patients with valvular disease initially or at follow-up were included.

‡These six patients had nine events.

firmed the presence of both infective and Libman-Sacks vegetations on the mitral valve and Libman-Sacks vegetations on the tricuspid valve. This patient subsequently died of sepsis.

Two patients without valvular disease had complications: one had a fatal hemorrhagic stroke and the other had fatal cardiac tamponade. One of the controls had a transient ischemic attack.

DISCUSSION

In our study, neither the presence of valvular disease nor changes in valvular disease over time were

temporally associated with the duration, activity or severity, or treatment of lupus. There are several possible explanations for the absence of any associations among these variables. The clinical and immunologic markers of activity in other organ systems may be present at a different time or have a different duration from those of valvulitis. Another possibility is that antiphospholipid antibodies, which are frequently present in patients with lupus independently of the activity or severity of the disease, may cause valvular injury.^{2,3,18} Furthermore, the many scoring systems based on clinical or laboratory variables for the assessment of the activity and severity of lupus may be limited in their accuracy.^{13,14,19-22}

An important finding in this study is that over time, valvular abnormalities frequently resolve or change, and new abnormalities often develop. Valvulitis, like inflammation in other organ systems, is probably intermittent. Several pathological studies of patients with lupus have shown active and healed valvulitis, as well as active Libman-Sacks vegetations with acute thrombus, healed vegetations with or without hyalinized thrombus, or both active and healed vegetations, in the same or different valves.²³⁻²⁵ Thrombotic vegetations due to a hypercoagulable state have also been demonstrated in patients with lupus.²⁶⁻²⁹ These vegetations cannot be clearly differentiated from Libman-Sacks vegetations on echocardiography.^{30,31} In addition, valvular vegetations can embolize, which may result in a change in their appearance or resolution.^{7,28,29,32}

In our study, most of the complications were related to valvular disease. All five patients with ischemic strokes or peripheral embolism had valvular disease. Cerebral vasculitis was suspected in one patient and confirmed in another, but both patients also had valvular vegetations. The patient with pathological confirmation of cerebral vasculitis had multiple small cerebral infarcts and both infective and Libman-Sacks vegetations on the mitral valve. Cerebral vasculitis and cardioembolism may therefore have coexisted in these two patients. Cardioembolism was the more likely diagnosis in the other three patients with stable disease, because cerebritis and vasculitis usually occur in patients with highly active disease. Other echocardiographic and pathological studies have reported a 10 to 20 percent incidence of ischemic stroke in patients with lupus,^{7,29,32} with valvular vegetations, valvulitis, or left-heart thrombus identified as the cardioembolic substrate in 70 to 90 percent of the patients. None of the patients in these studies had cerebral vasculitis,^{29,32} and none of the patients treated with anticoagulants had recurrent events.⁷

Infective endocarditis was an important cause of morbidity and mortality in three of our patients. It was the initial presentation in two patients and was complicated by severe valvular dysfunction, heart failure, and death from sepsis in two. The three pa-

tients with endocarditis had had disease flares requiring high doses of corticosteroids and cytotoxic agents shortly before their infections developed. Infection is the most common cause of death in patients with lupus, and the risk is highest among those with active disease treated with high doses of corticosteroids or cytotoxic agents.^{33,34} Antibody-mediated granulocyte dysfunction, leukopenia, hypocomplementemia, abnormal immunoglobulin synthesis, and functional asplenia are possible pathogenic factors.³³⁻³⁵ Infection can also mimic, accompany, or trigger a flare of the disease.

The mortality rate at five years and the causes of death (cardiac, cerebrovascular, and infectious) in our study are similar to those in other studies.^{1-3,32,36-38} In our study, however, heart disease was responsible for six of the seven deaths: severe valvular and coronary artery disease in two patients, infective endocarditis in two, cardiac tamponade in one, and intracerebral bleeding during anticoagulant therapy for a prosthetic valve in one. We cannot rule out the possibility that a selection bias in the study population contributed to this association.

Our results differ from those of studies using transthoracic echocardiography.^{1-3,32,36,37} In these studies, the prevalence of valvular disease was less than 40 percent, which may be related to the use of a less sensitive echocardiographic technique. Valvular abnormalities were also reported to be persistent or progressive in these studies. The inclusion of patients older than 60 years of age or a higher proportion of inpatients may explain this finding. As in our study, four of these studies found no association between valvular disease and indicators of the activity of lupus.^{1,32,36,37}

The clinical course of lupus frequently fluctuates between periods of remission and flares, and valvular disease may parallel these clinical changes. The treatment of lupus is also generally initiated or modified according to its clinical features. Our study yielded an unexpected finding: neither the usual clinical and immunologic markers of the activity of lupus nor its treatment appeared to be temporally related to the presence of or changes in valvular disease. Therefore, in a patient with stable lupus, newly diagnosed valvular disease may not reflect an increase in the activity or severity of the lupus, and there may be no need to modify antiinflammatory therapy. In addition, the demonstration of valvular disease at one point in time is not predictive of permanent or progressive valvular dysfunction. Given the poor prognosis associated with infective endocarditis in patients with lupus, however, this complication should be looked for in febrile patients with active disease and clinically suspected or known valvular disease.

Since most patients with lupus and valvular disease have no cardiac symptoms, a careful cardiovascular examination should be the primary method of

screening for valvular regurgitation or stenosis in patients who may require echocardiography or antibiotic prophylaxis for infective endocarditis. In addition, since strokes in patients with lupus are frequent and valvular thickening and vegetations are prevalent and can serve as substrates for cardioembolism, prophylactic antiplatelet therapy may be appropriate for such patients, with the recognition that there is no evidence supporting the efficacy of antiplatelet therapy in this setting.

Long-term anticoagulation should be considered independently of the echocardiographic findings in patients with focal neurologic deficits or peripheral embolism and no features of systemic vasculitis. In contrast, if vasculitis or cerebritis is suspected in a patient with active disease, transesophageal echocardiography can be used to detect a cardioembolic substrate, and the findings can be used as the basis for treatment with anticoagulants instead of or in addition to high-dose corticosteroids and cytotoxic agents. Finally, in patients with lupus and recurrent systemic embolism, the surgical excision of uninfected valvular vegetations may not prevent their recurrence.

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REFERENCES

- Galve E, Candell-Riera J, Pigrau C, Permanyer-Miralda G, Garcia-Del-Castillo H, Soler-Soler J. Prevalence, morphologic types, and evolution of cardiac valvular disease in systemic lupus erythematosus. *N Engl J Med* 1988;319:817-23.
- Khamashta M, Cervera R, Asherson RA, et al. Association of antibodies against phospholipids with heart valve disease in systemic lupus erythematosus. *Lancet* 1990;335:1541-4.
- Nihoyannopoulos P, Gomez PM, Joshi J, Loizou S, Walport MJ, Oakley CM. Cardiac abnormalities in systemic lupus erythematosus: association with raised anticardiolipin antibodies. *Circulation* 1990;82:369-75.
- Roldan CA, Shively BK, Lau CC, Gurule FT, Smith EA, Crawford MH. Systemic lupus erythematosus valve disease by transesophageal echocardiography and the role of antiphospholipid antibodies. *J Am Coll Cardiol* 1992;20:1127-34.
- Dajce H, Hurley EJ, Szarnicki RJ. Cardiac valve replacement in systemic lupus erythematosus: a review. *J Thorac Cardiovasc Surg* 1983;85:718-26.
- Lehman TJ, Palmeri ST, Hastings C, Klippel JH, Plotz PH. Bacterial endocarditis complicating systemic lupus erythematosus. *J Rheumatol* 1983;10:655-8.
- Futrell N, Millikan C. Frequency, etiology, and prevention of stroke in patients with systemic lupus erythematosus. *Stroke* 1989;20:583-91.
- Wei JY. Age and the cardiovascular system. *N Engl J Med* 1992;327:1735-9.
- Seward JB, Khandheria BK, Oh JK, et al. Transesophageal echocardiography: technique, anatomic correlations, implementation, and clinical applications. *Mayo Clin Proc* 1988;63:649-80.
- Castello R, Lenzen P, Aguirre F, Labovitz AJ. Quantitation of mitral regurgitation by transesophageal echocardiography with Doppler color flow mapping: correlation with cardiac catheterization. *J Am Coll Cardiol* 1992;19:1516-21.
- Perry GJ, Helmcke F, Nanda NC, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. *J Am Coll Cardiol* 1987;9:952-9.

12. Currie PJ, Seward JB, Reeder GS, et al. Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation* 1985;71:1162-9.
13. Urowitz MB, Gladman DD, Tozman ECS, Goldsmith CH. The Lupus Activity Criteria Count (LACC). *J Rheumatol* 1984;11:783-7.
14. Katz JD, Senecal JL, Rivest C, Goulet JR, Rothfield N. A simple severity of disease index for systemic lupus erythematosus. *Lupus* 1993;2:119-23.
15. StatXact 3 for Windows user manual. Cambridge, Mass.: CYTEL Software, 1995 (software).
16. SAS/STAT user's guide, version 6. Cary, N.C.: SAS Institute, 1990.
17. The measurement of interrater agreement. In: Fleiss JL. *Statistical methods for rates and proportions*. 2nd ed. New York: John Wiley, 1981:212-36.
18. Hojnik M, George J, Ziporen L, Shoenfeld Y. Heart valve involvement (Libman-Sacks endocarditis) in the antiphospholipid syndrome. *Circulation* 1996;93:1579-87.
19. Hay E, Gordon C, Emery P. Assessment of lupus: where are we now? *Ann Rheum Dis* 1993;52:169-72.
20. Liang MH, Socher SA, Roberts WN, Esdaile JM. Measurement of systemic lupus erythematosus activity in clinical research. *Arthritis Rheum* 1988;31:817-23.
21. Belmont HM, Hopkins P, Edelson HS, et al. Complement activation during systemic lupus erythematosus: C3a and C5a anaphylatoxins circulate during exacerbations of disease. *Arthritis Rheum* 1986;29:1085-9.
22. Porcel JM, Ordi J, Castro-Salomo A, et al. The value of complement activation products in the assessment of systemic lupus erythematosus flares. *Clin Immunol Immunopathol* 1995;74:283-8.
23. Libman E, Sacks B. A hitherto undescribed form of valvular and mural endocarditis. *Arch Intern Med* 1924;33:701-37.
24. Klemperer P, Pollack AD, Baehr G. Pathology of disseminated lupus erythematosus. *Arch Pathol* 1941;32:569-631.
25. Bulkley BH, Roberts WC. The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy: a study of 36 necropsy patients. *Am J Med* 1975;58:243-64.
26. Bidani AK, Roberts JL, Schwartz MM, Lewis EJ. Immunopathology of cardiac lesions in fatal systemic lupus erythematosus. *Am J Med* 1980;69:849-58.
27. Deppisch LM, Fayemi AO. Non-bacterial thrombotic endocarditis: clinicopathologic correlations. *Am Heart J* 1976;92:723-9.
28. Gorelick PB, Rusinowitz MS, Tiku M, McDonald LW, Robbins L. Embolic stroke complicating systemic lupus erythematosus. *Arch Neurol* 1985;42:813-5.
29. Devinsky O, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. *Ann Neurol* 1988;23:380-4.
30. Blanchard DG, Ross RS, Dittrich HC. Nonbacterial thrombotic endocarditis: assessment by transesophageal echocardiography. *Chest* 1992;102:954-6.
31. Lopez JA, Fishbein MC, Siegel RJ. Echocardiographic features of non-bacterial thrombotic endocarditis. *Am J Cardiol* 1987;59:478-80.
32. Sturfelt G, Eskilsson J, Nived O, Truedsson L, Valind S. Cardiovascular disease in systemic lupus erythematosus: a study of 75 patients from a defined population. *Medicine (Baltimore)* 1992;71:216-23.
33. Hellmann DB, Petri M, Whiting-O'Keefe Q. Fatal infections in systemic lupus erythematosus: the role of opportunistic organisms. *Medicine (Baltimore)* 1987;66:341-8.
34. Nived O, Sturfelt G, Wollheim F. Systemic lupus erythematosus and infection: a controlled and prospective study including an epidemiological group. *Q J Med* 1985;55:271-87.
35. Piliero P, Furie R. Functional asplenia in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990;20:185-9.
36. Ong ML, Veerapen K, Chambers JB, Lim MN, Manivasagar M, Wang F. Cardiac abnormalities in systemic lupus erythematosus: prevalence and relationship to disease activity. *Int J Cardiol* 1992;34:69-74.
37. Leung WH, Wong KL, Lau CP, Wong CK, Cheng CH. Cardiac abnormalities in systemic lupus erythematosus: a prospective M-mode, cross-sectional and Doppler echocardiographic study. *Int J Cardiol* 1990;27:367-75.
38. Estes D, Christian CL. The natural history of systemic lupus erythematosus by prospective analysis. *Medicine (Baltimore)* 1971;50:85-95.