Cardiac Abnormalities in Systemic Lupus Erythematosus

Association With Raised Anticardiolipin Antibodies

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Two-dimensional echocardiographic studies were prospectively performed in 93 patients with systemic lupus erythematosus (SLE) to discover the incidence and spectrum of cardiac abnormalities and to relate these findings to the presence of high levels of anticardiolipin antibodies. Assessment of the intracardiac anatomy was also performed in an additional 12 patients who had increased anticardiolipin antibody levels but did not have SLE. Fifty patients (54%) with SLE had cardiac abnormalities, and 43 patients (46%) had normal hearts. Three categories of cardiac abnormalities were identified—valvular lesions, ranging from vegetations to valvular thickening, were found in 28%, pericardial effusion or thickening was found in 20%, and regional or global left ventricular dysfunction was found in 5%. High levels of anticardiolipin antibodies were detected in 50 patients (54%) with SLE. Of those, only 11 (22%) had an entirely normal heart, whereas the remaining 39 (78%) had at least one cardiac abnormality (valvular lesions in 20, pericardial effusion in 15, and myocardial dysfunction in five patients). In patients with SLE, the presence of abnormal intracardiac anatomy was strongly associated with increased levels of anticardiolipin antibodies ($p<0.0001$). The overall sensitivity and specificity of high levels of anticardiolipin antibodies in the prediction of cardiac abnormalities was 78% and 74%, respectively, with a positive predictive accuracy of 78% and a negative predictive accuracy of 74%. Eight of the 12 patients (67%) who had increased anticardiolipin antibodies but whose disease did not fulfill the American Rheumatism Association classification criteria for SLE had cardiac abnormalities similar to those in patients with SLE compared with only four (33%) who had normal hearts ($p<0.001$). High levels of anticardiolipin antibodies are strongly associated ($p<0.0001$) with cardiac abnormalities, not only in SLE but also in other lupuslike syndromes. (Circulation 1990;82:369–375)

The heart is a major target for disease in patients with systemic lupus erythematosus (SLE). Several clinical and postmortem studies have demonstrated a high incidence of cardiovascular manifestations involving the pericardium, myocardium, endocardium, cardiac valves, and coronary vessels.1–7 Although the association of raised anticardiolipin antibodies with SLE and other lupuslike syndromes has been well described,8–13 there is little prospective data on their possible role in the development of cardiovascular abnormalities.14 There are now a few reports15–18 describing an association between valvular lesions and raised anticardiolipin antibodies in patients with SLE, but the spectrum of cardiac pathology and the predictive value of high levels of anticardiolipin antibodies to the presence of cardiac involvement have not been fully established.

With increased use of two-dimensional echocardiography and Doppler techniques, the spectrum of cardiac pathology can readily be detected in the living population with SLE.19,20 The aim of this study was to prospectively describe the incidence of cardiac involvement using two-dimensional and Doppler echocardiographic studies and to relate the findings to the presence or absence of anticardiolipin antibodies.

Methods

Ninety-three consecutive patients with SLE fulfilling revised American Rheumatism Association criteria21 for the diagnosis were referred to the echocardiography laboratory between July 1982 and

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TABLE 1. Patients With Increased Anticardiolipin Antibodies and No Lupus Erythematosus

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Anticardiolipin antibodies</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High levels (9–100 ELISA units)</td>
<td>Very high levels (&gt;100 ELISA units)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary APS</td>
<td>5</td>
<td>1</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>2</td>
<td>0</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>SLE-like</td>
<td>1</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1</td>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>2</td>
<td></td>
<td>12</td>
</tr>
</tbody>
</table>

APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

August 1989, where they were examined by personnel blinded to the clinical and biochemical findings. There were 84 female and nine male patients with a median age of 32 years (range, 15–70 years). Fourteen patients had mild systemic hypertension secondary to renal involvement.

An additional group of 12 patients with increased anticardiolipin antibodies in whom the diagnosis of SLE had not been met according to American Rheumatism Association revised criteria were evaluated for comparison. These patients were women with a median age of 36 years (range, 22–64 years) (Table 1). Primary antiphospholipid syndrome was defined as the occurrence of recurrent thrombosis, recurrent fetal loss, or thrombocytopenia with raised levels of anticardiolipin antibodies in the absence of SLE or other defined disease.12,22

Two-dimensional echocardiographic and Doppler studies were also performed in a control group of 40 age- and sex-matched healthy subjects. Thirty-six were women and four were men with a mean age of 35 years (median, 33 years; range, 25–65 years). All normal subjects had a normal clinical examination; none was hypertensive or diabetic.

Cardiac catheterization with coronary angiography was performed in all patients with suspected coronary artery occlusion or clinical or echocardiographic evidence of myocardial dysfunction.

Echocardiography and Doppler

All studies were performed with a Toshiba Sonolayer SSH-65A or SSH-160A phased-array ultrasound system. A 3.75-MHz transducer was used for two-dimensional echocardiographic imaging, and a 2.5-MHz transducer was used for pulsed and continuous wave Doppler and color flow imaging. Studies were recorded on a 3/4-in. video tape recorder for subsequent review and frame-by-frame analysis.

Two-dimensional echocardiographic examination was first performed according to a standardized protocol.23 All studies were performed by technicians who were aware of the referral diagnosis, but the recorded study was read blindly by a cardiologist expert in echocardiography to ensure objectivity.

Particular attention was paid to the mitral and aortic valve leaflets and subvalvular apparatus. Left ventricular function was assessed from long-axis and serial short-axis projections for the detection of regional wall motion abnormalities.

Abnormal echocardiographic findings were described as pericardial, valvar, or myocardial dysfunction. Pericardial abnormalities were described as pericardial effusion or thickening. Valvar lesions were grouped into three categories, none of which was present in the control group: 1) valvar vegetations as distinct localized masses of variable size seen on the surface of the valve leaflets, 2) diffuse valvar thickening producing either stenosis or regurgitation, and 3) localized thickening of part or all of a leaflet with impaired mobility producing regurgitation. Mitral prolapse or anular or valvar calcification were not considered part of the pathologic spectrum. Myocardial dysfunction was described as global or regional hypokinesis or akinesis. Finally, the presence or absence of intracardiac masses (thrombi) was also noted.

Doppler echocardiography was performed beginning with color flow imaging of the intracardiac cavities. The gain control was set immediately below the level at which a background color artifact was detected. Regurgitant jets were graded on a scale of from one to three.24 When abnormal intracardiac flow was detected, pulsed and continuous wave Doppler studies were performed to measure the maximal flow velocities. Valvar regurgitation seen only with Doppler and not associated with a murmur was considered "physiological."

Biochemical Profile

Blood was drawn within 1 week of the echocardiographic study. Anticardiolipin antibodies were measured by an enzyme-linked immunosorbent assay (ELISA) as previously described.25 Values are expressed in arbitrary ELISA units, with the upper limit of the normal range taken as 5 SDs above the normal mean value (9 units for IgG and 8 units for IgM26). Tests to detect the lupus anticoagulant and false-positive VDRL reactions were not routinely performed.

Follow-up Studies

Follow-up studies were performed in 65 of the 93 patients (70%) with SLE 1–7 years (mean, 3.2 years) after the initial study. These patients included 49 of the 51 (96%) with abnormal hearts and 16 of the 43 (37%) with clinically and echocardiographically normal hearts.

Statistical Analysis

Morphological echocardiographic findings as well as ventricular function were related to the presence or absence of high anticardiolipin antibody levels by the $\chi^2$ test (with Yates' correction when indicated). A p value of less than 0.05 was considered significant.

The predictive value of increased anticardiolipin antibodies as an indicator of cardiac involvement was
determined by calculating the sensitivity and specificity as well as the predictive accuracies.

Results

Ninety-three patients had SLE. Forty-three (46%) had normal cardiac anatomy (Table 2). Twenty-six (28%) had valvular involvement. Eight patients had valvular vegetations, and 18 other patients showed leaflet thickening, reduced mobility, stenosis, or regurgitation. Twenty patients (21%) had pericardial effusion (19 patients) or thickening (one patient), and five other patients had regional or diffuse myocardial dysfunction. One patient with myocardial dysfunction also had a small pericardial effusion. Abnormal intracardiac anatomy was strongly associated with increased anticardiolipin antibodies ($\chi^2=27.3, p<0.0001$) (Table 2). Conversely, patients with normal intracardiac anatomy were unlikely to have increased anticardiolipin antibodies. The overall sensitivity and specificity of high levels of anticardiolipin antibodies in the prediction of cardiac abnormalities was 78% and 74%, respectively, with a positive predictive accuracy of 78% and a negative predictive accuracy of 74%.

Echocardiographic and Doppler Findings in Control Group

Good-quality recordings were obtained in all subjects. Two had mild posterior mitral annular calcification, whereas four other patients had short, localized echogenic areas at the leaflet tips (three aortic and one mitral) that did not affect the linear outline of the leaflet or its movement. Color Doppler showed small regurgitant jets (mitral in one and aortic in two) originating from the leaflet's coaptation line and extending for less than 2 cm into the cavity. Five of these individuals were more than 55 years old, and none had any audible murmurs. Consequently, these echocardiographic and Doppler characteristics were considered part of the normal range of valve appearances, more frequently encountered in older subjects. In addition, a small mitral regurgitant jet was visualized in four subjects less than 50 years old and was located immediately behind the posterior mitral leaflet.

Patients With SLE and Increased Anticardiolipin Antibodies

Valvular lesions. Fifty patients (54%) with SLE had increased anticardiolipin antibodies, seven (14%) of whom had values of more than 100 ELISA units (Table 2). Twenty patients (40%) had at least one definite valvular abnormality. Seven patients had valvular vegetations on the mitral valve, whereas one other patient had vegetations on the aortic valve, at the commissures between the left and right coronary cusps, and immediately below the valve, producing a 55 mm Hg gradient across the left ventricular outflow tract. Vegetations on the mitral valve usually appeared as small (2×4 mm), sessile, and irregular wartlike echodensities that were attached at the middle portion of the atrial surface of the leaflets and not interfering with valve mobility. In one patient, both leaflets were massively involved by vegetations on the ventricular surfaces. The posterior leaflet was almost entirely tethered to the posterior wall. A large (10×16 mm), homogeneous, and irregular mass was firmly attached at the midportion of the ventricular surface of the anterior leaflet without affecting the leaflet's mobility (Figure 1). Two patients with valvular vegetations had severe mitral regurgitation requiring valve replacement, whereas three other patients had diffuse thickening of the leaflets leading to mild (two patients) or moderate (one patient) mitral stenosis with calculated effective orifice areas of 2.1, 2.4, and 1.4 cm², respectively. In these patients, the valve appearance mimics the morphological changes seen in rheumatic mitral stenosis (commissural fusion, diastolic doming of the anterior leaflet, and fixed posterior leaflet); however, in contrast to rheumatic valves, the leaflet thickening was diffuse, the chordae tendinae were normal, and small vegetations were seen on the atrial surface of the leaflets, proximally.

Twelve other patients did not have vegetations but did have diffuse thickening with decreased mobility, leading to valve dysfunction in four (one stenosis and three moderate regurgitation). None of these patients had abnormalities similar to those present in patients with rheumatic valve disease. Although the valvular thickening was more discrete in the remaining eight patients, it was clearly distinct from the short, local-
Parastemal long-axis view of the heart from a patient with systemic lupus erythematosus and high levels of anticardiolipin antibodies. A massive vegetation on ventricular surface of the anterior mitral leaflet (arrows) not interfering with the valve mobility, is clearly visualized. LA, left atrium; LV, left ventricle; RVO, right ventricular outflow.

ized echogenic areas on the leaflet tips seen in the normal subjects; in each of these patients, mild mitral regurgitation was audible clinically and visible on color flow imaging. These findings were distinct from mitral anular calcification, which was an additional finding in three patients more than 60 years old.

Four of the seven patients with very high (>100 ELISA units) anticardiolipin antibodies had significant valvular lesions. Two had vegetations, and two had thickened mitral leaflets with mild regurgitation. Only one patient had a clinically and echocardiographically normal heart.

**Myocardial dysfunction.** Five patients had left ventricular dysfunction (Table 2); they were all young (<39 years) and had increased anticardiolipin antibodies. In four patients, there was a regional akinetis segment, implying myocardial infarction. Three patients had anteroapical left ventricular akinesis with an organized thrombus and one inferior akinesis. At cardiac catheterization, three patients had total occlusion of the left anterior descending coronary artery with no atheromatous changes, and another patient with extensive inferior akinesis had a normal coronary arteriogram. One other patient had diffuse ventricular hypokinesis with normal left ventricular end-diastolic dimensions that returned to normal after steroid treatment.

**Pericardial abnormalities.** Forty-eight of the 93 patients (52%) with SLE had clinical evidence of pericarditis at one stage of their illness. Only 20 of these patients (42%) had echocardiographic evidence of pericardial involvement, 15 of whom had increased anticardiolipin antibodies (Table 2). Nineteen patients had small pericardial effusions, and one had pericardial thickening. None of these patients had any clinical or echocardiographic evidence of tamponade or constriction. One patient had both a small pericardial effusion and localized mitral valve thickening.

**Patients With SLE and Absence of Increased Levels of Anticardiolipin Antibodies**

Forty-three patients (46%) with SLE did not have elevated levels of anticardiolipin antibodies (Table 2). Six patients (14%) had a definite valvular thickening at the mitral (four patients) or aortic valve (two patients), producing mild valvular regurgitation (detected both clinically and with color Doppler). Another five patients (12%) had a small pericardial effusion. Thirty-two patients (74%) had entirely normal hearts.
TABLE 3. Patients With High (>9 ELISA units) Levels of Anticardiolipin Antibodies and Associated Cardiac Abnormalities

<table>
<thead>
<tr>
<th>Patients</th>
<th>Patients with a normal heart (n) (%)</th>
<th>Patients with an abnormal heart (n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLE (n=50)</td>
<td>11 (22)</td>
<td>39 (78)</td>
</tr>
<tr>
<td>No SLE (n=12)</td>
<td>4 (33)</td>
<td>8 (67)</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus.
χ² (with Yates’ correction)=0.2, df=1, p=NS.

Type and Prevalence of Cardiac Involvement in Patients Without SLE Who Had Increased Anticardiolipin Antibodies

Twelve patients with increased anticardiolipin antibodies did not meet the revised American Rheumatology Association criteria for lupus erythematosus (Table 2). Four patients (33%) had normal hearts. Of the remaining eight (67%), four had mitral valve vegetations similar to those previously described (three with primary antiphospholipid syndrome and one with vasculitis). Another patient with vasculitis had severe aortic regurgitation requiring surgery. Two patients with paraneoplastic syndromes had localized mitral valve thickening with mild mitral regurgitation detected both clinically and with Doppler. Another patient had a markedly thickened and irregular valve with severe mitral regurgitation requiring surgery.

There was no difference in the frequency of cardiac involvement between patients with increased anticardiolipin antibodies in SLE and those with lupuslike syndromes (Table 3).

Follow-up Studies

During the course of the study, none of the patients died. Vegetations remained unchanged in the majority of patients. In one patient, massive vegetations on the mitral valve progressively decreased in size and mitral regurgitation showed an associated decrease during 2 years of immunosuppressive treatment. Another patient with small vegetations on both mitral leaflets and diminished mobility producing mild mitral stenosis showed a progressive decrease in effective mitral valve area (from 2.1 to 1.3 cm² during 3 years).

The patient with inferior left ventricular akinesis and normal coronary arteriograms developed recurrent chest pain while on immunosuppressive treatment with azathioprine and prednisolone. Echocardiography 4 years later showed a markedly dilated left ventricle with extensive anteroapical akinesis in addition to the existing inferior akinesis. Repeat coronary angiography revealed extensive disease involving all major coronary arteries. (This patient has been reported elsewhere.)

None of the patients with SLE and normal intracardiac anatomy who were restudied (16 of 43 patients) showed any change in their echocardiographic or Doppler findings during the follow-up period.

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.3,5,28,29 These data do not necessarily reflect the prevalence of cardiovascular involvement in the living population. Echocardiography provides a readily available non-invasive technique that can be used to identify the spectrum of cardiac abnormalities. In the only prospective echocardiographic study, Galve et al29 found clinically significant valvular lesions in 18% of the patients but did not examine the prevalence of nonvalvular cardiac involvement. In the present study, the overall prevalence of cardiac involvement in patients with SLE was 58%. The most common pathology was valvular (28%), ranging from thickened leaflets with impaired valve function (20%) to vegetations (9%), followed by pericardial involvement (21%) and myocardial dysfunction (5%).

In line with previous reports,19 we have identified a wide spectrum of valvular lesions. In the present study, small, localized echogenic areas on the leaflets not affecting function were not regarded as abnormal because similar patterns were seen in the control group, particularly in the older patients. Equally important but difficult is to separate physiological from pathological valvular regurgitation. In the present study, Doppler regurgitation not associated with a murmur was not considered pathological. Physiological regurgitation in normal subjects may form a prerequisite for the later development of pathological regurgitation, so a clear borderline between the two may be difficult to determine. Diffuse thickening of one or more leaflets was the most common valvular lesion and was invariably associated with valve dysfunction, leading to regurgitation or stenosis. Libman-Sacks vegetations are the hallmark of cardiac involvement in patients with SLE. In the present study, all vegetations were distinct, of variable size, and firmly attached to the proximal or middle portion of the leaflets and did not exhibit any independent movement. We believe that this echocardiographic description may distinguish Libman-Sacks vegetations from infected vegetations of infective endocarditis, which are often pedunculated, located at the leaflet tips, and have an associated chaotic, flopping motion. If sterile Libman-Sacks vegetations become infected, the two cannot be separated echocardiographically.

Microscopically, these vegetations consist of proliferating and degenerating cells, fibrin, fibrous tissue, and occasional hematoxylin bodies. There may be a variable amount of inflammation with a scattering of plasma and large mononuclear cells. In a study addressing the immunology of cardiac involvement in patients with lupus, Bidani et al28 reported that the lesions of Libman-Sacks endocarditis contain immunoglobulins and complement. All of our patients with SLE who had distinct vegetations and...
67% of our patients who had thickened valves had high levels of antiphospholipid antibodies. Interestingly, 67% of our patients with increased antiphospholipid antibodies who did not have lupus had similar valvular abnormalities, further supporting the hypothesis that valvular deformity and dysfunction could have an immunemediated postinflammatory basis.

Although the first symptom of illness in SLE is often acute, painful pericarditis or relapsing pericarditis with intermittent pain, friction, and effusion, echocardiography is an insensitive technique for diagnosing pericarditis when it is not accompanied by effusion or thickening; only 42% of the patients with previous pericarditis had abnormal echocardiographic findings.

A raised prevalence of antibodies to phospholipids in patients with SLE has been recognized for many years, and assays for these include the false-positive VDRL, the lupus anticoagulant, and antibodies to cardiolipin. In patients with SLE, antiphospholipid antibodies have been particularly associated with venous and arterial thrombosis,8,10 recurrent fetal loss,11 pulmonary hypertension,8 endocardial disease,13 seizures, and migraine.12 In the present study, we found that a high proportion of patients with cardiac disease and SLE also had increased antiphospholipid antibodies; this provides support for the theory that cardiac involvement is mediated by antiphospholipid antibodies, possibly due to a primary stimulation of vascular endothelium by immunologic factors.30 Although the mechanism remains uncertain, it is relevant that the same spectrum of valvular abnormalities seen in SLE occurs in patients with increased antiphospholipid antibodies without other features of SLE. These results, although highly suggestive, do not establish a causal link between antiphospholipid antibodies and cardiac damage.

The relation of antiphospholipid antibodies to coronary thrombosis is intriguing. There is a raised incidence of myocardial infarction among patients with SLE, and this is an important cause of death.31 The possibility that intimal proliferation and enhanced atherogenesis are due to a primary stimulation of vascular endothelium by immunologic factors has been supported by an experimental animal model.32

High density lipoproteins are reduced in patients with active SLE, and treatment with steroids is associated with increased low density lipoproteins and triglyceride concentrations.33,34 All our patients with thrombotic coronary artery occlusion had increased antiphospholipid antibodies, and a 25-year-old patient with normal coronary arteriogram at initial presentation developed extensive coronary artery disease47 that was angiographically indistinguishable from extensive atheroma.

Myocardial involvement is also well known in patients with SLE,6 and one of our patients showed myocardial dysfunction that became normal after immunosuppressive treatment. Fulminant myocarditis, however, is rare, even in autopsy series comprising patients who presumably had the most severe disease. Nonspecific perivascular infiltration with lymphocytes and neutrophils is often observed, but intimal proliferation of the smaller intramyocardial arteries, hyalinized vessels, and recanalized vessels are also often-reported features.2,3 Echocardiography can readily depict left ventricular wall motion abnormalities and identify the presence of intraventricular thrombus formation, but because both premature coronary atherosclerosis and arteritis may occur in patients with SLE, coronary arteriography is necessary to document the presence of coronary artery disease. Focal myocardial necrosis resulting from small-vessel arteritis is not likely to produce major regional wall motion abnormalities, such as occur after occlusion of a major coronary artery branch. It may, however, contribute to global depression of left ventricular function.

In summary, in the present study the presence of increased antiphospholipid antibodies was strongly associated with cardiac pathology. High levels of antiphospholipid antibodies were found in significantly more patients with SLE who had abnormal cardiac anatomy detected by two-dimensional echocardiography. Other patients with increased antiphospholipid antibodies who did not meet the diagnostic criteria for SLE showed the same spectrum of cardiac pathology. It is suggested that there may be a causal link between high levels of antiphospholipid antibodies and cardiac damage; this may be important in guiding therapeutic decisions.

References


**KEY WORDS** • echocardiography • Libman-Sacks endocarditis • systemic lupus erythematosus
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