JACC Vol. 18, No. 4
October 1991:931–6

Cardiac Involvement in Patients With Primary Antiphospholipid Syndrome

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To evaluate cardiac involvement in primary antiphospholipid syndrome, two-dimensional and Doppler echocardiographic studies were performed in 34 consecutive patients with this syndrome. All patients had an increased level of serum anticardiolipin antibodies with no evidence of malignancy or systemic lupus erythematosus. The clinical manifestations of primary antiphospholipid syndrome were arterial thrombosis in 14 patients, venous thrombosis in 6 and recurrent fetal loss in 14. Valvular lesions were observed on two-dimensional echocardiography in 11 patients (32%) (9 women and 2 men), aged 24 to 57 years (mean ± 1 SD 36 ± 10).

Abnormal echocardiographic findings were observed in 9 (64%) of 14 patients with arterial thrombosis versus 1 (17%) of 6 patients with venous thrombosis and 1 (7%) of 14 patients with recurrent fetal loss. The most common echocardiographic abnormality was mitral leaflet thickening, found in five patients; this was associated with mitral regurgitation in three and with combined mild mitral stenosis and regurgitation in one patient. Localized subvalvular mitral thickening was observed in one patient and calcification of the annulus in another. Aortic valve thickening was observed in two patients, one of whom also had a moderate degree of aortic regurgitation. Vegetation-like lesions on the mitral or aortic valve were found in two patients.

It is concluded that valvular lesions are commonly found in primary antiphospholipid syndrome, particularly when the syndrome is manifested by peripheral arterial thrombosis. The location and appearance of valvular lesions in this syndrome are heterogeneous. Most patients have no clinically significant valvular disease. Two-dimensional and Doppler echocardiographic studies are often informative in these patients.

(J Am Coll Cardiol 1991;18:931–6)

An elevated serum level of antiphospholipid antibodies has been associated with thromboembolic phenomena in patients with an autoimmune disease such as systemic lupus erythematosus or in those with a malignant tumor (1). Other patients with an autoimmune disease and increased serum antiphospholipid antibodies have no diagnostic criteria for systemic lupus erythematosus (2) and no evidence for malignancy and therefore this group has been classified as having primary antiphospholipid syndrome (3). Clinical manifestations of this syndrome are recurrent fetal loss or arterial and venous thrombosis (3,4). However, the reason for the appearance of a vascular complication in a given patient with primary antiphospholipid syndrome is unclear.

Cardiac valvular lesions have been reported (5–11) in nonhomogeneous groups of patients with systemic lupus erythematosus and lupus-like syndromes. The present study was undertaken to evaluate the frequency and characteristics of valvular lesions in patients with primary antiphospholipid syndrome and to determine whether such lesions are correlate with thromboembolic phenomena.

Methods

Study patients. The study group included 34 consecutive patients with the primary antiphospholipid syndrome diagnosed and followed up in the hematology and obstetrics clinics at the Rambam Medical Center. There were 29 women and 5 men, whose mean age (±1 SD) was 36 ± 13 years.

Twenty patients were referred because of vascular manifestations. Arterial thrombosis was found in 14 patients (cerebrovascular accident or transient ischemic attack in 9 patients and femoropopliteal obstruction in 5). Venous thrombotic manifestations were deep vein thrombosis in six patients, including two with pulmonary embolism. In 14 young women, the reason for serum anticardiolipin antibodies examination was three or more early or late abortions, intrauterine fetal death or premature delivery. The patients' history was carefully examined to exclude rheumatic heart disease and bacterial endocarditis.

As a control group, 22 consecutive patients with clinically suspected embolic arterial occlusion (cerebrovascular accident in 20 and femoropopliteal obstruction in 2) without overt heart disease were studied. These patients were re-

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Manuscript received December 4, 1990; revised manuscript received February 15, 1991, accepted April 23, 1991.

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0735-1097/91/$3.50

ferred for echocardiography for the detection of occult embolic sources during the corresponding 6-month period of the study. They included 17 men and 5 women whose age ranged from 30 to 81 years (mean ± 1 SD 57 ± 14).

Laboratory criteria for evidence of antiphospholipid antibodies. These included increased (>20 U) serum levels of immunoglobulin G (IgG) anticardiolipin antibodies as assessed by enzyme-linked immunosorbent assay (according to Harris et al. [12]) and presence of lupus anticoagulant as defined by a positive diluted thromboplastin titration index >1.3 at 1/200 final dilution (13).

Two-dimensional and Doppler echocardiography. All echocardiographic studies were performed by one experienced operator (S.A.R.) who was unaware of the patients' clinical information. Two-dimensional and pulsed Doppler echocardiographic images were acquired with a Hewlett-Packard 77020A ultrasound imager equipped with a 2.5-MHz phased array transducer. Continuous wave Doppler recordings were obtained with a 1.9-MHz nonimaging transducer connected to the Hewlett-Packard imager. Standard two-dimensional and M-mode echocardiographic images were obtained in the parasternal, apical and subcostal views and recorded on a 0.5-in. (1.27 cm) videotape with VHS format.

The presence of mitral or tricuspid regurgitation was defined as a systolic high velocity jet that extended from the valve into the corresponding atrium. The left and right atria were carefully scanned to identify the maximal extent of the regurgitant jet. Aortic regurgitation was defined as a diastolic high velocity jet that extended from the aortic valve into the left ventricular outflow tract. The left ventricle was scanned by using apical views to identify the maximal extent of the regurgitant jet.

The continuous wave Doppler transducer was placed at the apical position and optimally angulated according to the sound beam to record the mitral, aortic and tricuspid valve flow velocities.

Data Analysis

Echocardiographic evaluation of valve morphology. The morphologic features of the mitral valve were characterized according to leaflet thickening and motion and the structure of the subvalvular apparatus. Thickening of mitral leaflets >5 mm noted on multiple echocardiographic views was defined as abnormal (14). A localized and mobile echogenic mass on an otherwise normal-appearing valve was defined as a vegetation-like lesion.

Grading of valvular regurgitation by Doppler ultrasound. To assess the severity of mitral and tricuspid regurgitation, the extent of the systolic jet into the left and the right atrium, respectively, was evaluated. Mild regurgitation was defined when the regurgitant jet extended into less than half of the atrium. Moderate regurgitation was defined when the jet extended into >50% of the atrium and severe regurgitation when filling of the entire atrium was observed (15).

Aortic valve regurgitation was graded according to the extension of the regurgitant jet into the left ventricular outflow tract. Mild aortic regurgitation was defined as a diastolic jet detected below the tip of the anterior mitral leaflet. In moderate aortic regurgitation, the jet extended below the tip of the anterior mitral leaflet, whereas in severe aortic regurgitation, it extended beyond the papillary muscles (16).

Doppler calculations. Mitral valve area was calculated as 220/(pressure half-time) (17). Peak pressure gradients were calculated from peak velocities with use of the modified Bernoulli equation ($\Delta P = 4V^2$), where P = pressure and V = volume (18). Mean pressure gradients were obtained by planimetry with use of the software package of the Hewlett-Packard 77020A ultrasound imager.

Results

Patient characteristics. Valvular lesions were observed on two-dimensional echocardiography in 11 (32%) of the 34 patients (9 women and 2 men) whose age ranged from 24 to 57 years (mean ± 1 SD 36 ± 10).

Demographic, clinical and echocardiographic characteristics of the patients with primary antiphospholipid syndrome and valvular lesions are summarized in Table 1. The age of patients with a valvular lesion was not significantly different from that of patients without a valvular lesion (36 ± 10 vs. 34 ± 10 years, respectively; p = NS by unpaired Student's *t* test).

Correlation of valvular lesions with the clinical manifestations of primary antiphospholipid syndrome. An abnormal echocardiographic study was found in 9 (64%) of the 14 patients with arterial thrombosis compared with only 1 (17%) of 6 patients with venous thrombosis and 1 (7%) of 14 patients with recurrent fetal loss ($p < 0.01$ arterial thrombosis vs. venous thrombosis; $p < 0.001$ arterial thrombosis vs. fetal loss by difference of two proportions). In the control group, only 1 (4.5%) of 22 patients had a vegetation on the mitral valve.

Echocardiographic appearance of valvular lesions. The mitral valve was most commonly involved, with echocardiographic abnormalities found in eight patients. Several patterns of mitral valve involvement were observed. The most common pattern found in five patients was leaflet thickening. In one patient (Patient 1), a 24-year old woman, leaflet motion was restricted, resulting in mild mitral stenosis and regurgitation (mitral valve area 1.9 cm^2 calculated by the pressure half-time method) (Fig. 1).

Three other patterns of mitral disease were found, each in one patient. Figure 2 is a tracing from a 39-year old man with localized thickening of the mitral apparatus at the chordal level. Another 27-year old woman (Patient 8) had a heavily calcified mitral anulus with severe mitral regurgitation and left ventricular and left atrial enlargement. A distinctive pattern of mitral disease was a vegetation-like lesion. Figure 3 presents a tracing from a 28-year old woman (Patient 5)

Table 1. Clinical and Echocardiographic Characteristics of 11 Patients With Primary Antiphospholipid Syndrome and Valvular Lesions

Pt No.	Age (yr)/ Gender	Clinical	Echocardiography	
			2-D	Doppler
1	24/F	Art T	MVT	Mild MR, MS
2	36/F	Art T	MVT, LAE	Mod MR
3	57/F	Art T	MVT	Mild MR, TR, AR
4	39/M	Art T	Sub MVT	Mild MR
5	28/F	Art T	MV veg	Mod MR
6	31/F	Art T	MVT	Mild MR
7	43/M	Art T	AVT	
8	37/F	Art T	MAC, LVE	Severe MR
9	42/F	Art T	AVT	Mod AR
10	43/F	Venous T	AV veg	
11	31/F	Fetal loss	MVT	

AR = aortic regurgitation; Art = arterial; AVT = aortic valve thickening; AV veg = aortic valve vegetation; Doppler = Doppler echocardiography; F = female; LAE = left atrial enlargement; LVE = left ventricular enlargement; M = male; MAC = mitral anulus calcification; Mod = moderate; MR = mitral regurgitation; MS = mitral stenosis; MVT = mitral valve thickening; MV veg = mitral valve vegetation; Pt = patient; Sub = subvalvular; T = thrombosis; TR = tricuspid regurgitation; 2-D = two-dimensional.

with a mobile echogenic mass attached to the posterior leaflet of the mitral valve.

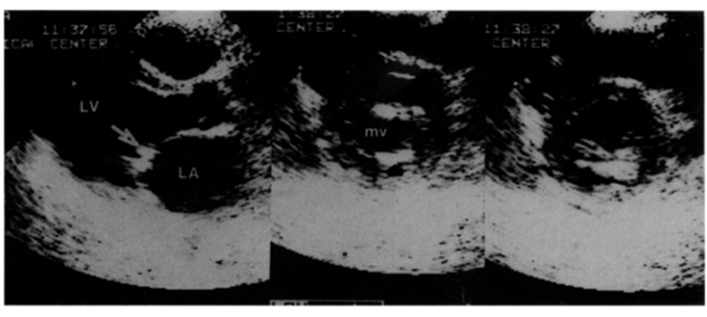
Mitral lesions were typically associated with some degree of mitral regurgitation on Doppler echocardiography in seven (88%) of eight patients. Regurgitation was mild in four patients, moderate in two and severe in one. The patient with severe mitral regurgitation had congestive heart failure treated with digoxin and diuretic drugs.

Aortic valve involvement was found in three patients. Aortic valve thickening was found in two patients (Patients 7 and 9). In both patients, the aortic valve had three cusps and the thickening was more prominent at the base of the cusps (Fig. 4). In a 43-year old woman (Patient 10), a vegetation-like, echogenic and mobile lesion prolapsing into the left ventricular outflow tract during diastole was observed on the noncoronary cusp. Moderate aortic regurgitation was recorded in one of the three patients with an aortic valve lesion; all three were >40 years of age.

Discussion

Prevalence of valvular lesions in patients with primary antiphospholipid syndrome. The present study demonstrates that cardiac valve abnormalities are common in patients with primary antiphospholipid syndrome. We observed an overall

Figure 1. Patient 1. Echocardiograms in the parasternal long-axis view (left panel) and short-axis views in diastole (middle panel) and systole (right panel) in a 24-year old woman. Marked thickening of the mitral leaflets is noted (white arrow) with restricted motion in diastole, resulting in combined mild mitral regurgitation and stenosis. LA = left atrium; LV = left ventricle; mv = mitral valve.



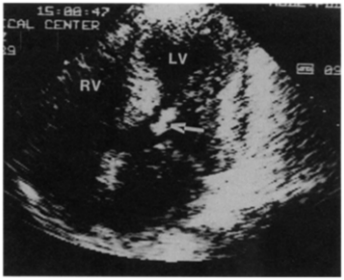


Figure 2. Patient 2. Apical four-chamber view in a 39-year old man. Thickening of the subvalvular mitral apparatus with fusion of chordae tendineae is noted (white arrow). RV = right ventricle; other abbreviations as in Figure 1.

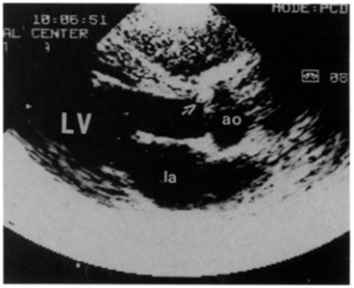


Figure 4. Patient 9. Parasternal long-axis view in a 42-year old woman. Thickening of the basal portion of the right aortic cusp is noted (white arrow). This patient had a moderate degree of aortic (ao) regurgitation. Abbreviations as in Figure 3.

32% incidence of cardiac involvement. Similar results have been observed by other investigators (5,11).

This incidence of valvular abnormalities in patients with primary antiphospholipid syndrome is significantly higher than the incidence noted in patients with idiopathic systemic thromboembolism. Although our control patients were significantly older than the study patients, only one control patient had a lesion on the mitral valve. Similar data regarding the yield of echocardiography in idiopathic systemic thromboembolism have been published by Lovett et al. (19) from the Mayo Clinic.

Echocardiographic appearance of valvular lesions in primary antiphospholipid syndrome. In 1924, Libman and Sacks (20) described vegetations that were free of bacteria. They introduced the term "atypical verrucous endocarditis," later related to systemic lupus erythematosus. Bacteria-free verrucae have been recognized in other conditions, such as debilitating states and malignancies, frequently termed "nonbacterial thrombotic endocarditis." These lesions most frequently appear on left-sided valves, but can be found on the valvular ring, chordae tendineae or any other location of ventricular or atrial endocardium (20,21).

Granulation tissue may thicken and deform the valve during the healing process. Although this deformation is rarely clinically significant, cases with severe valvular regurgitation requiring valve replacement have been reported (22,23). There is a remarkable similarity in the location and echocardiographic appearance of valvular lesions in patients with the nonbacterial thrombotic endocarditis just described and those of the valvular lesions found in our study patients.

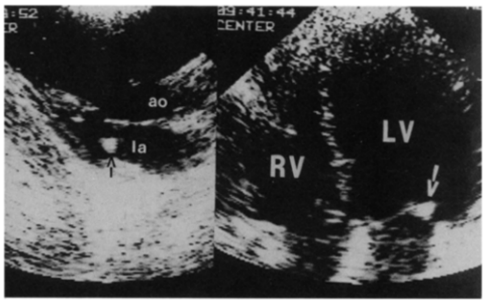


Figure 3. Patient 5. Parasternal long-axis view (left panel) and apical four-chamber view (right panel) in a 28-year old woman. A vegetation-like mobile and echogenic mass is attached to the posterior mitral leaflet (arrows). ao = aorta; la = left atrium; other abbreviations as in Figures 1 and 2.

Although no patient had a history of rheumatic fever, the possibility of coincidental rheumatic heart disease in patients with primary antiphospholipid syndrome has been considered. The echocardiographic appearance of valvular lesions in primary antiphospholipid syndrome is remarkably different from that in rheumatic valvular disease. In our patients with primary antiphospholipid syndrome and mitral valve disease, there was no commisural fusion or valve doming and posterior leaflet motion was unrestricted. Subvalvular mitral disease, commonly seen in rheumatic heart disease, was found in only one patient (Fig. 2) and had a very unusual morphology that was atypical for rheumatic mitral disease.

Aortic valve thickening in patients with primary antiphospholipid syndrome was more prominent at the base of the cusp. No patient had combined aortic and mitral valve lesions commonly seen in rheumatic heart disease.

Clinical manifestations of patients with primary antiphospholipid syndrome. Patients with cardiac valvular lesions were typically young women. However, gender and age in this group did not differ from those in patients with primary antiphospholipid syndrome without cardiac involvement. Our findings demonstrate a clear preponderance of valvular lesions whenever primary antiphospholipid syndrome is manifested by arterial thrombosis. An abnormal echocardiographic study was found in 9 (64%) of 14 patients with arterial thrombosis compared with 17% of patients with venous thrombosis and 7% of patients with fetal loss only.

The pathogenesis of thrombosis in patients with primary antiphospholipid syndrome has not yet been elucidated. Suggested potential mechanisms for thrombosis include increased platelet activity, decreased antithrombin III plasma levels, inhibition of prostacyclin release from vascular endothelial cells and inhibition of the protein C-protein S thrombomodulin system (24,25). In addition, impaired fibrinolysis manifested by decreased tissue plasminogen activator release from endothelial cells and increased plasminogen activator inhibitor have recently (26) been observed in patients with primary antiphospholipid syndrome. However, these abnormalities have been reported in a minority of patients and cannot yet predict whether a particular patient with primary antiphospholipid syndrome will develop thromboembolism.

Valvular endothelial damage may result from the turbulence and jet effect that are most prominent in the left side of the heart. In normal persons, antithrombotic mechanisms prevent the formation of thrombus on the injured endothelium. As discussed, patients with primary antiphospholipid syndrome may have impaired antithrombotic mechanisms leading to platelet and fibrin deposition.

The nonspecific nature of the platelet-fibrin thrombus is emphasized by its occurrence as a result of numerous types of stress or injury. This explains why valvular lesions in primary antiphospholipid syndrome have a location and appearance similar to those in other diseases with associated nonbacterial thrombotic endocarditis.

Although endothelial damage may explain both endocardial and local peripheral arterial thrombosis, it is still unclear whether cardiac valvular lesions may be the origin of peripheral arterial embolism in primary antiphospholipid syndrome.

Conclusions. Mitral and aortic valve lesions are commonly found in the primary antiphospholipid syndrome, particularly when manifested by peripheral arterial thrombosis. Most patients have no clinically significant valvular disease. The location and appearance of valvular lesions in primary antiphospholipid syndrome are not specific. Similar lesions can be found in other diseases with nonbacterial thrombotic endocarditis. Two-dimensional and Doppler echocardiographic techniques are often informative in detecting valvular involvement in primary antiphospholipid syndrome.

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