Background and Purpose—Although thromboembolic events are the major complication of primary antiphospholipid syndrome (PAPS), cardiac involvement is commonly present. Left atrial appendage (LAA) is recognized as an important source for thrombus formation and thromboembolism. The purpose of the study was to assess the structure and function of LAA with transesophageal echocardiography (TEE) in PAPS patients.

Methods—Thirty-one PAPS patients (22 women, mean age 36 ± 9 years) in sinus rhythm and 31 (17 women, mean age 37 ± 7 years) controls with normal TEE examination were investigated.

Results—Eighty-four percent of the PAPS patients had functional and structural valvular defect predominantly in the mitral valve. Valvular lesions were especially frequent in PAPS patients with a history of cerebrovascular events, patients with history of arterial thrombosis (91.6%), and patients with high titers of IgG antiphospholipid antibodies (100%). Intracardiac thrombus was present in 5 patients and in 1 of them it was located in LAA. The structure of LAA was similar between groups. Left atrial appendix ejection fraction (51.8 ± 4 versus 48.6 ± 5.5%; P < 0.05) and LAA peak outflow velocity (87 ± 10.9 versus 80.6 ± 10.3 cm/s; P = 0.02) was significantly higher in PAPS group compared with controls. In PAPS patients with mitral regurgitation (MR), LAA outflow peak velocity (84.3 ± 10 versus 98.6 ± 6.5 cm/s; P = 0.002) and LAA inflow peak velocity (67.8 ± 10.5 versus 80.8 ± 8.6 cm/s; P = 0.009) were significantly lower compared with PAPS patients without MR.

Conclusions—It was concluded that disease process in PAPS frequently involved cardiac valves especially mitral valve but spared LAA function. LAA function was normal, but intracardiac thrombus was present in 5 patients and 1 of them was located in LAA. MR in PAPS patients seems to impair LAA function. (Stroke. 2005;36:592-596.)

Key Words: antiphospholipid syndrome ■ echocardiography ■ embolism ■ venous thrombosis

Antiphospholipid syndrome is a clinical entity with arterial and venous thrombosis, recurrent abortion and/or thrombocytopenia, and high titer of antiphospholipid antibodies. If there is no underlying cause like systemic lupus erythematosus, the disease is called primary antiphospholipid syndrome (PAPS).¹

Recent studies indicated the presence of impaired cardiac valvular function, intracardiac thrombus, and coronary artery disease in PAPS patients.²⁻³ Thromboembolism from an intracardiac thrombus is a major cause of ischemic strokes.⁴ Overlooked before the advent of transesophageal echocardiography (TEE), structural and functional changes in left atrial appendage (LAA) have been related to local thrombus formation and systemic embolization.⁵⁻⁶ In different patient groups examined with TEE, intimate relation between LAA functions, spontaneous echo contrast, and thromboembolic events were revealed.⁷

There are only a few studies assessing cardiac involvement in PAPS with TEE, and none of these studies assessed LAA function. The purpose of the study is to examine LAA structure and function and cardiac involvement with TEE.

Materials and Methods

Thirty-one PAPS patients in sinus rhythm (22 women, mean age 36 ± 9 years) diagnosed according to diagnostic criteria defined by Wilson et al⁴ were examined. Patients with malar rash, discoid rash, oral ulceration, arthritis, pleurisy, pericarditis, proteinuria ≥0.5 g/d; lymphopenia, anti-dsDNA, anti-ENA–positive, and ANA titers ≥1:320 were excluded. Twelve patients had a history of arterial thrombosis (38.7%), and 17 patients (54.8%) had history of venous thrombosis.

In 27 patients (87%), lupus anticoagulant tests were positive. According to the standardized anticardiolipin antibody test by Harris et al,⁶ 16 (51.6%) patients had elevated anticardiolipin IgM and 18 (58.1%) had moderate or high titers of anticardiolipin IgG. Ten patients (32%) were using acetylsalicylic acid, 15 patients (48%)...
TABLE 1. Demographic and Echocardiographic Characteristics of Patients and Controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>31</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>36.7±9 (18–56)</td>
<td>37±7.6 (22–56)</td>
<td>NS</td>
</tr>
<tr>
<td>Women, %</td>
<td>71</td>
<td>55</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac rhythm</td>
<td>Sinus</td>
<td>Sinus</td>
<td></td>
</tr>
<tr>
<td>LVIdd, mm</td>
<td>47.5±4</td>
<td>46.5±2</td>
<td>NS</td>
</tr>
<tr>
<td>LVIdsm, mm</td>
<td>29.3±5</td>
<td>28.4±2</td>
<td>NS</td>
</tr>
<tr>
<td>IVSd, mm</td>
<td>9.4±1</td>
<td>9.3±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>PWDd, mm</td>
<td>9±1</td>
<td>9±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>68.3±9</td>
<td>69.3±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>31.9±3.3</td>
<td>31.1±1.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

IVSd indicates interventricular septum diastolic diameter; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVIdd, left ventricular diastolic diameter; LVIdsm, left ventricular systolic diameter; NS, not significant; PWDd, posterior wall diastolic diameter.

Serologic Determination
Anticardiolipin IgG and IgM antibodies (ACA) were assessed by enzyme-linked immunosorbent assay. Enzyme-linked immunosorbent assay was performed by using a commercial kit as part of the routine evaluation of the patients, and cutoff points were determined by using local controls. Samples of 0 to 10 GPL or MPL units were regarded as negative, 11 to 19 U were regarded as low positive, 20 to 60 U were regarded as positive, and over 60 U regarded as high positive for both ACA–IgG and ACA–IgM. Lupus anticoagulant (LA) was diagnosed according to the published criteria. Fresh citrated venous blood samples were used for LA testing. All plasma samples were centrifuged at 2000g for 15 minutes, filtered through 0.22-μ filters, and both the activated partial thromboplastin time (aPTT) and the kaolin clotting time were measured twice. The results were compared with those of filtered normal pooled plasma, which was collected from at least 10 normal controls. The aPTT and kaolin clotting times were considered to be prolonged if they were >3 standard deviations longer than the controls (39 seconds for aPTT, 88 seconds for kaolin clotting time). In mixing studies, the patients’ plasmas were mixed 1:1 with normal pooled plasma, and both the aPTT and kaolin clotting times were performed on all samples. Frozen thawed platelets were used for the platelet neutralization test. Complete correction was obtained in all LA-positive samples. The LA and ACA tests were repeated at least 2 months after the initial determination.

Transthoracic Echocardiography
Transthroacic echocardiographic examination was performed using a 100-cm gasroscope tipped by a 5-MHz “phased array” multi-plane probe with “pulsed,” “continuous wave,” and “color Doppler” capabilities (attached to a standard Vingmed System Five, Norway). The procedure was performed after 6 hours of fasting according to the locally modified standard protocol. Valve abnormalities were classified into 3 principal categories: leaflet thickening, nodule, and valve regurgitation or stenosis. Abnormal leaflet thickening was considered present when a leaflet showed a thickness >3 mm for the mitral valve and >2 mm for the aortic valve. A nodule was defined as an abnormal localized echodensity with well-defined borders either as part of or adjacent to valve leaflets. The diameter of the nodule on the 2-dimensional image was determined. It was considered macronodule if the diameter of the nodule was >5 mm. Grading of regurgitation severity was based on the size of the Doppler color flow jet. It was mild if the jet extended only 1 to 2 cm and persisted throughout the regurgitant period. It was moderate if the jet was >2 cm and occupied up to 50% of the atrial or left ventricular outflow tract area. It was severe if the jet was >2 cm and occupied up to 75% of the atrial or left ventricular outflow tract area. In 70% of the cases, the principal axis of the LAA was markedly bent or spiral, which accounts for some of the differences in shape and size of the LAA in vivo when viewed with TEE in different imaging planes. Thus, it was examined from different angles (0°, 45°, 90°, and 135°). The angle from which LAA was best imaged like a crescent (45°±10°) was recorded on VHS cassette for offline measurements. All of the offline measurements were performed using the same echocardiography unit. The LAA peak area (A_{max}) was measured before electrocardiographic P wave, and minimum area (A_{min}) was measured after the QRS wave with planimetry. The LAA ejection fraction (EF) was calculated with the formula:

\[ \text{LAAEF} = \left( \frac{A_{\text{max}} - A_{\text{min}}}{A_{\text{max}}} \right) \times 100 \]

The LAA opening diameter and length were also measured and blood flows in and out of LAA were recorded. All parameters were measured twice during different cardiac cycles and the mean value was used.

Statistics
Statistical analysis was performed with a commercially available statistical package Statistical Package for Social Sciences for Windows version 10.0 (SPSS Inc) and Microsoft Excel Version 5.0. Numerical variables were reported as mean±standard deviation. Differences between means of 2 groups were assessed with Student’s t test. Nonparametric variables were reported as counts and percents and statistical differences between groups were assessed with χ² test. For 2×2 contingency tables, Yates correction was performed, and when assumptions were violated for 2×2 contingency tables, Fisher exact test was used. P<0.05 was accepted as significant.

Transesophageal Echocardiography
Transesophageal echocardiographic examination was performed using a 100-cm gasroscope tipped by a 5-MHz “phased array” multi-plane probe with “pulsed,” “continuous wave,” and “color Doppler” capabilities (attached to a standard Vingmed System Five, Norway). The procedure was performed after 6 hours of fasting according to the locally modified standard protocol. Valve abnormalities were classified into 3 principal categories: leaflet thickening, nodule, and valve regurgitation or stenosis. Abnormal leaflet thickening was considered present when a leaflet showed a thickness >3 mm for the mitral valve and >2 mm for the aortic valve. A nodule was defined as an abnormal localized echodensity with well-defined borders either as part of or adjacent to valve leaflets. The diameter of the nodule on the 2-dimensional image was determined. It was considered macronodule if the diameter of the nodule was >5 mm. Grading of regurgitation severity was based on the size of the Doppler color flow jet. It was mild if the jet extended only 1 to 2 cm and persisted throughout the regurgitant period. It was moderate if the jet was >2 cm and occupied up to 50% of the atrial or left ventricular outflow tract area. It was severe if the jet was >2 cm and occupied up to 75% of the atrial or left ventricular outflow tract area. In 70% of the cases, the principal axis of the LAA was markedly bent or spiral, which accounts for some of the differences in shape and size of the LAA in vivo when viewed with TEE in different imaging planes. Thus, it was examined from different angles (0°, 45°, 90°, and 135°). The angle from which LAA was best imaged like a crescent (45°±10°) was recorded on VHS cassette for offline measurements. All of the offline measurements were performed using the same echocardiography unit. The LAA peak area (A_{max}) was measured before electrocardiographic P wave, and minimum area (A_{min}) was measured after the QRS wave with planimetry. The LAA ejection fraction (EF) was calculated with the formula:

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The LAA opening diameter and length were also measured and blood flows in and out of LAA were recorded. All parameters were measured twice during different cardiac cycles and the mean value was used.

Results
Clinical features in patients with PAPS are shown in Table 2. The most common presenting manifestations were thrombocytopenia (64.5%) and deep vein thrombosis (45.1%). Twenty-six (83.8%) patients had cardiac involvement. Mitral regurgitation (MR) was the most predominant findings. Twelve patients (38.7%) had mild, 11 patients (35.5%) had moderate, and 1 patient (3.2%) had severe MR. Only 1 patient had mild mitral stenosis. Three patients (9.6%) had mild

Twelve patients (38.7%) had mild, 11 patients (35.5%) had moderate, and 1 patient (3.2%) had severe MR. Only 1 patient had mild mitral stenosis. Three patients (9.6%) had mild
aortic insufficiency and 1 (3.2%) patient had moderate tricuspid insufficiency.

**Structural Valve Lesions**

Eighteen PAPS patients (58%) had structural valve lesions; 8 (25.8%) PAPS patients had only valvular thickening, 2 (6.45%) had micronodules, 1 (3.2%) had macronodules, 4 (12.9%) had valvular thickening and micronodules, and 3 (9.6%) had valvular thickening and macronodules (Figure 1). In 13 (41.9%) PAPS patients, no valvular lesion was discernible. Most of the lesions seen were on the anterior cusp of the mitral valve.

**Relation Between Valvular Lesions and Clinical Findings**

All 8 patients with stroke (25.8%) had valvular involvement. Eleven of the 12 patients (91.6%) with a history of arterial embolism and 13 (76%) of the 17 patients with a history of venous thrombosis had valvular involvement. Structural valvular lesions were present in 9 (52.6%) of the 17 cases with a history of venous thrombosis, and this ratio was 9 of 12 (75%) in patients with arterial thrombosis. All 7 (22.5%) patients with high-titer anticardiolipin IgG levels had valvular involvement.

**Presence of Intracardiac Thrombus**

Thrombus was present in 5 patients: in the right atrium in 2 (6.4%) patients, in the right ventricle in 1 (3.2%) patient, in the LAA (Figure 2) in 1 (3.2%) patient, and in the left ventricle in 1 (3.2%) patient. The presence of LAA thrombus was not previously reported meriting a detailed description. This patient was a 31-year-old man with high-titer anticardiolipin IgG positivity (98 GPL U/mL). On echocardiographic examination, left atrial and ventricular dimensions were within normal limits, a micronodule was present in the left coronary cusp of the aortic valve, and there was no MR. The LAA EF was significantly low (44%); the outflow and filling peak velocity (PV) of the LAA were 58 cm/s and 68 cm/s, respectively.

**Assessment of LAA Function**

On echocardiographic assessment, LAA dimensions were similar between PAPS patients and controls with no statistically significant difference between groups for LAA length, ostium diameter, LAAmax, and LAAmin. The LAA EF was significantly higher in the PAPS patients compared with controls (51.8±4% versus 48.6±5.5%; P<0.05) (Table 3).

**LAA Doppler Analysis**

The LAA outflow PV was significantly higher in PAPS group compared with controls. The velocity time integral (VTI) of LAA outflow, LAA filling PV and VTI, and LAA early diastolic PV were similar in PAPS patients and controls (Table 3).

**LAA Function in the Different Patient Groups**

In arterial thrombus and stroke groups, LAA EF was 52±2.1% and 51.3±1.6%, respectively, and higher than the control group. In the venous thrombosis group, the LAA EF was 51.5±4.9% and similar to controls. When LAA flows were assessed, LAA outflow PV and VTI were similar in PAPS patients with history of stroke or arterial embolism compared with controls, but higher in PAPS patients with history of venous embolism compared with controls. The LAA filling PV and VTI were similar in PAPS patients with

| TABLE 3. Results of Left Atrial Appendage Structure and Flow Parameters in Patient and Control Groups |
|----------------------------------------------------------|-----------|----------------|
| LAA ostium diameter, mm                                  | 19±3.4    | 19.2±2.4       | NS         |
| LAA length, mm                                           | 31.6±3.8  | 31.7±4.9       | NS         |
| LAA maximum area, mm²                                     | 35±7.5    | 33.8±9         | NS         |
| LAA minimum area, mm²                                     | 16.8±3.4  | 17.2±4.6       | NS         |
| LAA EF, %                                                | 51.8±.4   | 48.6±5.5       | <0.05      |
| LAA outflow PV, cm/sn                                     | 87±10.9   | 80.6±10.3      | 0.02       |
| LAA outflow VTI, cm                                       | 5.1±.05   | 5±0.6          | NS         |
| LAA filling PV, cm/sn                                     | 70.3±11.3 | 66±9.6         | NS         |
| LAA filling VTI, cm                                       | 4.8±.6    | 4.6±0.6        | NS         |
| LAA early diastolic PV, cm/sn                             | 26.6±5.5  | 25.1±4.5       | NS         |

EF indicates ejection fraction; LAA, left atrial appendage; NS, not significant; PV, peak velocity; VTI, velocity time integral.
history of stroke and arterial and venous thrombosis compared with controls.

When PAPS patients with (24 patients) or without (7 patients) MR were compared, $\Delta_{\text{LAAmax}}$, $\Delta_{\text{LAAmin}}$, and LAA-EF were similar between groups. The LAA outflow PV and filling PV were significantly higher in PAPS patients without MR compared with PAPS patients with MR (98.6±6.5 versus 84.3±10 cm/s, $P=0.002$; 80.8±8.6 versus 67.8±10.5 cm/s, $P=0.009$). The LAA early diastolic PV was 30.3±6.6 cm/s in PAPS patients without MR and 25.7±5 cm/s in PAPS patients with MR without reaching statistical significance.

Discussion

Previous studies with echocardiography revealed the occurrence of endocardial involvement and valvular lesions in systemic lupus erythematosus and the association of these lesions with antiphospholipid antibodies. These studies led the attention to the investigation of patients with primary antiphospholipid syndrome for endocardial lesions. The incidence of cardiac involvement was reported to be 10% to 60% in studies performed with transthoracic echocardiography, but recent studies performed with TEE revealed higher rates of cardiac involvement (82% to 75.9%). The lesions described were mitral insufficiency, cusp thickening, micronodules, and macroonodule formation on the cusps.

In our study, cardiac involvement was present in 83.8% of the PAPS patients. Major finding was the presence of MR (77.4%). Only 1 patient had mild mitral stenosis. Valvular lesions were present in all stroke patients and in most of the patients with history of arterial or venous thrombosis indicating that cardiac involvement may increase the risk for cerebral thrombosis. Because antiphospholipid antibody titers were high in PAPS patients with cardiac involvement, there may be a relationship between these 2 events. Espinola et al reported similar findings in a study with TEE. Valvular involvement was present in 75.9% of the patients and the most frequent lesion was the presence of MR (59%). Arterial and venous thrombotic events were more frequent in patients with valvular anomalies. Brenner et al similarly reported increased valvular involvement in patients with history of arterial thrombosis.

Endothelial disruption during the normal wear and tear of cardiac valve structures and the insufficiency of antithrombotic mechanisms in PAPS patients may combine to create the cardiac involvement delineated. Accordingly, deposition of fibrin–platelet and thrombin on the valve might be the initiating event, after which organization, valvular fibrosis, and distortion results in the functional impairment of the cardiac valve. The mechanism by which antiphospholipid antibody causes valvular impairment is not understood. The antibodies are thought to contribute to the formation of thrombus on the valvular endothelium.

Turiel et al in a study of 40 PAPS patients reported a correlation between valvular thickening and antiphospholipid antibody titers. The incidence of valvular involvement in patients with high-titer IgG antibodies was similar to our study. Thrombus formation in cardiac cavities was another observation in PAPS patients. Contrary to valvular involvement that was mostly on the left side, thrombus formation was observed more frequently on the right side of the heart. We also noted the presence of a thrombus in LAA previously not reported in the literature. No study was undertaken to examine LAA in PAPS patients despite the fact that it is a major source of thrombi. In recent studies that examine LAA function and flow patterns, 3 parameters were chosen to assess LAA structure and function, LAA volume, flow pattern, and flow velocities. In our study, LAA of PAPS patients were found structurally similar to the control group; however, LAA flow velocities and LAA EF were higher, indicating that LAA was hyperkinetic in this group of patients. It was also interesting to find a LAA thrombus in a structurally normal LAA. We suggest that in the search of an embolic source in PAPS patients, LAA should be examined especially in patients with stroke. There is little information on the effect of MR on LAA function. Hemodynamically significant MR will dilate left atrium and LAA and cause increased filling pressures, and hence may result in impaired LAA function. These findings though contradictory had been reported in small studies. In our study, LAA outflow and filling PV were lower in patients with MR compared with patients without MR. These findings suggest that MR in PAPS, by impairing LAA function, might contribute to the formation of thrombus.

In conclusion, PAPS caused increased incidence of valvular lesions, among which MR was the most frequent. Valvular involvement was increased in patients with a history of arterial thrombus and thrombus formation was shown in all chambers of the heart. The LAA functions in PAPS patients were unaffected and were even hyperkinetic. Thrombus formation was observed in LAA, and the presence of MR adversely affected LAA function.

References


Assessment of Cardiac Structure and Left Atrial Appendage Functions in Primary Antiphospholipid Syndrome: A Transesophageal Echocardiographic Study
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