Antiphospholipid syndrome is an autoimmune disorder characterized by the presence of antiphospholipid antibodies, hypercoagulability, vascular thrombosis, and recurrent fetal loss. Cardiac involvement occurs frequently. Leaflet thickening and vegetations are detected quite often echocardiographically, but hemodynamically significant stenotic and/or regurgitant valvular disease is uncommon. Antiphospholipid syndrome can also cause left and right ventricular systolic and diastolic dysfunction as well as pulmonary hypertension. Other findings include spontaneous echo contrast and in situ mural thrombosis. In this review, the author discusses the major cardiac manifestations of antiphospholipid syndrome and highlights the role of echocardiography in their detection. (J Am Soc Echocardiogr 2009;22:1100-8.)

Keywords: Antiphospholipid syndrome, Echocardiography, Nonbacterial thrombotic endocarditis, Libman-Sacks endocarditis

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by hypercoagulability, vascular thrombosis, and fetal loss accompanied by antiphospholipid antibodies (APLAs). The most clinically relevant APLAs include anti-β2-glycoprotein 1 antibodies, antiphospholipid antibodies, and lupus anticoagulant. APLAs are normally present in low titers in a small percentage of otherwise healthy subjects, and they can become transiently elevated following a variety of infections. Definitive diagnosis of APS, however, requires the demonstration of persistently elevated titers.

Because of its vascular nature, the clinical features of APS are quite diverse and can affect a number of different organ systems (Table 1). There are 3 clinically distinct forms of the disease: primary, secondary, and catastrophic. Primary APS (PAPS) occurs in the absence of any underlying disorder. Disease occurring in the setting of other autoimmune disorders, most commonly systemic lupus erythematosus (SLE), is referred to as secondary APS (SAPS). The least common form, catastrophic APS (CAPS), is characterized by simultaneous thrombotic events occurring in multiple organ systems. Cardiovascular manifestations are common in all forms of APS. The purpose of this article is to review these along with their salient echocardiographic features.

PATHOGENESIS

Hypercoagulability in APS is mediated by APLAs. This term is a misnomer, because APLAs bind phospholipids rather weakly. They do, however, bind to the proteins to which phospholipids are complexed. These phospholipid moieties are believed to render their attached proteins antigenic by inducing conformational changes in them. APLAs bind to a number of clotting cascade factors or their regulatory proteins (Figure 1). In so doing, normal protein kinetics become deranged, resulting in a hypercoagulable state. Among the many clotting system proteins that have been shown to bind APLAs are β2-glycoprotein I, prothrombin, protein C, and protein S.

The pathologic expression of hypercoagulability in APS can take a variety of forms. The most common is in situ thrombosis of large veins. In situ arterial thrombosis also occurs, although far less often. Diffuse small vessel thrombosis (thrombotic microangiopathy) is rare, but
it is characteristically present in patients with CAPS. In situ thrombosis within the heart’s chambers has also been reported. The most common cardiac abnormality in APS is nonbacterial thrombotic endocarditis which is characterized by adherent platelet-fibrin thrombi on the endocardial surface of valves. Although frequently used interchangeably, Libman-Sacks endocarditis, seen in SLE, is strictly speaking, a pathologically distinct entity. Unlike the bland lesions of APS, Libman-Sacks endocarditis is a true valvulitis, replete with inflammatory cell infiltration, albeit greatly attenuated by steroid therapy.

Recent research suggests that APLAs are proatherogenic and are associated with the development of premature atherosclerosis. A full discussion of the mechanisms underlying this association is beyond the scope of this review. It is worth emphasizing that steroids, commonly used in the treatment of SAPS, have been shown to impart an atherosclerotic risk independent of APLAs.

### VALVULAR DISEASE

**Primary APS**

PAPS most often affects the left-sided valves, especially the mitral. The most common echocardiographic abnormality is focussing on the occluder leaflet rather than the leaflet thickening itself. In 40% to 60% of patients, the leaflet thickness can increase up to 3 times that of normal control valves and correlates with anticardiolipin titers. Vegetations are seen less often. They may be solitary or multiple and occur in 10% to 40% of patients. They are typically irregular in shape and may or may not be mobile. Vegetations on the mitral valve generally form on its atrial surface. Aortic valve vegetations have been described on both the ventricular and the vascular surface of the valve. Many reports have described so-called “kissing lesions” located on the opposing lines of leaflet closure of both the mitral and aortic valves. Decreased leaflet mobility and subvalvular thickening are rarely seen. Hemodynamically significant valvular stenosis and/or regurgitation occurs in only 3% of cases. Thorombotic lesions occurring on bioprosthetic valves requiring reoperation have also been described.

There is a paucity of data documenting the echocardiographic response of PAPS valve disease to antithrombotic therapy. Although anecdotal reports have demonstrated echocardiographic resolution of valvular lesions with treatment, several small series have shown that these may not respond to, or may even progress despite therapy. Surgical intervention is rarely required, reflecting the lack of valve deformity characteristic of the disease. On the other hand, otherwise structurally normal valves with critically located vegetations, for example, on apposing surfaces of coaptation, can produce hemodynamically significant regurgitation by interfering with a valve’s closing mechanism. Should such vegetations remain refractory to medical therapy, surgical intervention may be the only alternative to relieve valvular insufficiency.

**Secondary APS**

The mitral valve is most commonly involved in SAPS, aortic valve involvement is less common, and right-sided valve involvement is rare. The most common echocardiographic abnormality is leaflet thickening. Estimated to occur in 30% to 70% of patients. Diffuse thickening may be accompanied by reduced leaflet mobility.
but significant valvular stenosis and/or regurgitation rarely occurs.\textsuperscript{35,37} Localized thickening is generally confined to the base or mid portion of the affected leaflet.\textsuperscript{35} Vegetations can be solitary or multiple and are estimated to occur in 10% to 40% of patients.\textsuperscript{17} Irregular shape, broad-based attachment, and immobility are all characteristically seen.\textsuperscript{35,38} Lesions are most typically located on the atrial surface of the mitral valve and the vascular side of the aortic valve, with a predilection for the leaflet base.\textsuperscript{15} Chordal involvement is rare. Roldan et al\textsuperscript{35} noted that the vegetations of SAPS frequently have a unique echogenicity characterized by a central region of high reflectance suggesting fibrosis and/or calcification. It is worth emphasizing that the early pathologic studies of Libman and Sacks\textsuperscript{39} demonstrated patterns of valvular involvement quite different from those described herein. These authors described more frequent tricuspid valve involvement as well as more common involvement of the ventricular surface of both the mitral (Figure 3) and aortic valves. Roldan et al\textsuperscript{35} attributed these differences to the effects of modern therapies used in SLE.

Treatment of SLE valve disease with steroids, cytotoxic agents, non-steroidal anti-inflammatory agents, antimalarial agents, and anticoagulants is not uniformly effective.\textsuperscript{37} As with PAPS, valve lesions may resolve or progress, and new ones frequently develop regardless of therapy (Figure 4). Fortunately, surgical intervention is rarely required.\textsuperscript{30} Shortened bioprosthetic valve durability as well as suboptimal valve repair results have also been reported.\textsuperscript{17}

APLAs occur in about one fourth of patients with SLE.\textsuperscript{40} A number of studies have sought to determine if their presence has any effect on the valve disease found in these patients. Despite different imaging modalities, varied definitions of APLA positivity and dissimilar characterizations of echocardiographic valve disease, most\textsuperscript{38,41,42} but not all\textsuperscript{35} studies suggest that they have a negative impact. In fact, Farzaneh-Far et al\textsuperscript{41} found that the likelihood of having moderate or severe mitral regurgitation was increased more than threefold in patients with APLAs. It has therefore been suggested that APLAs enhance the ambient autoimmune milieu in patients with lupus valvulitis.\textsuperscript{43}

Patients with SAPS have been shown to have a higher prevalence of echocardiographic valve disease than those with PAPS. Vianna et al\textsuperscript{29} attributed this to autoimmune phenomena specific to SLE. However, the absence of any correlation between echocardiographic valve disease and conventional markers of disease activity (eg, the lupus activity criteria count)\textsuperscript{37,44} does not seem to support this.

### Catastrophic APS

There are few reports documenting the echocardiographic findings of patients with CAPS. This may be related in part to the rapid clinical deterioration and high mortality seen in this disorder.\textsuperscript{6} Mitral and aortic valve involvement characterized by multiple vegetations studding these leaflets’ coaptation surfaces has been described (Figure 5).\textsuperscript{45} Small-vessel disease, with angiographically normal epicardial arteries, may result in focal or global ventricular dysfunction.\textsuperscript{6,46,47}

### Differential Diagnosis

The clinical and echocardiographic features of APS may at times require distinction from those of infective endocarditis (IE). In this respect, it is worth noting that transient, infection-related APLAs occur in 14% of patients with IE.\textsuperscript{7} Culture-negative patients presenting with fever, APLAs, and valvular vegetations (pseudo-IE) can therefore pose significant diagnostic and therapeutic challenges.\textsuperscript{48,49}

IE has a number of echocardiographic features that differentiate it from APS valve disease, already described (Table 2).\textsuperscript{35} The lesions of IE tend to be solitary, of uniform echogenicity, and highly mobile. They typically affect the atrial surface of the mitral valve. In contrast to APS, IE of the aortic valve almost always spares the
valve’s vascular surface. Unlike the sterile vegetations of APS, those due to IE can spread directly or hematogenously to other cardiac structures, resulting in satellite lesions, abscess formation, or chordal rupture.

Increased leaflet thickness and chordal lesions may be seen in both rheumatic heart disease and APS, but their echocardiographic appearances are nevertheless distinct. In rheumatic heart disease, increased leaflet thickness generally progresses from the free margins toward the leaflet base. Hence, disease confined to the base is unlikely. Rheumatic leaflets are also commonly calcified, fused at the commissures and dome in diastole. The chordae are typically thickened, fused and foreshortened in rheumatic heart disease. In contrast, discrete masses can be seen attached to otherwise normal chordal structures in APS.

Papillary fibroelastomas can also mimic the vegetations seen in APS. However, these are typically singular and mobile, with a characteristic shimmerring or vibratory appearance. They have been described on virtually all endocardial surfaces.

CARDIAC THROMBOEMBOLISM

The heart is an important source of systemic embolization in patients with APS. APS valve lesions are believed to have significant embolic potential. Indeed, Cervera et al demonstrated a >3-fold risk for cerebrovascular events in APS when structurally abnormal valves were present. Systemic embolization can also result from in situ mural thrombi. In one series, transesophageal echocardiography detected mural thrombus in 13% of subjects, all of who were in normal sinus rhythm, without evidence of structural or functional abnormalities known to promote local stasis.

The finding of spontaneous echo contrast (SEC) in APS is of particular interest. The mechanism of its formation in these patients is unclear. Recent work indicates that SEC is caused by reversible red cell agglutination produced by intracardiac stasis rather than by activation of the clotting cascade. In a series published by Turiel et al, SEC was detected in 11% of subjects on transesophageal echocardiography. None of these patients had predisposing structural heart disease (e.g., wall motion abnormalities, mitral stenosis, atrial fibrillation). These findings notwithstanding, transesophageal echocardiography can render SEC more prominent because it is performed using high-frequency transducers.

PULMONARY HYPERTENSION

The estimated prevalence of pulmonary hypertension is 3.5% and 1.8% in PAPS and SAPS, respectively. The most common cause is recurrent thromboembolism originating from the veins of the lower extremities, which is occasionally detected fortuitously during
echocardiographic examination as free-floating thrombus in transit. In situ mural thrombus in the right-heart chambers are another, albeit uncommon, source of pulmonary thromboembolism. In situ thrombosis of the pulmonary arteries can also cause pulmonary hypertension but occurs far less frequently than chronic thromboembolic disease. Regardless of its cause, pulmonary hypertension can over time result in right ventricular systolic failure and dilatation. The latter may cause tricuspid annular enlargement and leaflet malcoaptation, resulting in valvular regurgitation.

ABNORMALITIES OF VENTRICULAR FUNCTION

Wall motion abnormalities and left ventricular systolic dysfunction in APS can come about through several mechanisms. Myocardial infarction can result from epicardial atherosclerosis or from thrombotic small-vessel disease, particularly in patients with CAPS. Patients with SAPS can, in addition, develop segmental and global wall motion abnormalities from myocarditis and from coronary artery vasculitis. Tako-Tsubo cardiomyopathy has also been reported.

Several studies have demonstrated abnormalities in Doppler-derived left ventricular filling patterns in patients with PAPS unrelated to comorbidities known to affect diastolic function (eg, diabetes, hypertension, coronary artery disease, valve disease). The mechanism of this lusitropic dysfunction is not known, although ischemia caused by small-vessel thrombotic vasculopathy has been proposed. Left ventricular diastolic dysfunction in patients with APS has alternatively been attributed to increased aortic stiffness due to aortic atherosclerosis, commonly seen in this population. This is related to the rapid transmission of reflected waves in the noncompliant aorta, which, by increasing afterload, results in slowing of the rate of active left ventricular relaxation. It has also been proposed that left ventricular diastolic dysfunction in APS can result from pulmonary hypertension. It is thought that enlargement of the right ventricle, the result of chronic pressure overload, produces a leftward shift of septum (reverse Bernheim effect), thereby altering the compliance properties of the left ventricle. However, more recent work has challenged this notion, instead attributing the altered transmitral Doppler filling patterns seen in such patients to reduced left ventricular preload. Regardless of which is the case, thromboendarterectomy results in normalization of transmitral flow (Figure 6).

Figure 4 Serial transthoracic images from a patient with SLE. (A) Image obtained at time of presentation with multiple cerebral infarcts. There are two vegetations on the atrial surface of the mitral valve, one on the anterior mitral leaflet (AML) near its free margin, and another on the posterior mitral leaflet (PML) at its mid portion. Diffuse leaflet thickening is also present. (B) Image obtained 2 months later while the patient was being treated with steroids and cytotoxic agents shows resolution of the vegetations and improvement in leaflet thickening. (C) Image taken 20 months later shows recurrence of vegetations and increased leaflet thickness despite the absence of disease activity. (Reproduced with permission from N Engl J Med.)

CONCLUSION

APS is an immunothrombotic disorder characterized by multiple organ involvement. Cardiac disease occurs frequently and can take a variety of forms. Among these are valve disease, occlusive coronary arterial disease, in situ cardiac thrombosis, ventricular dysfunction, and pulmonary hypertension. Echocardiography remains invaluable in their detection.
Figure 5 Short-axis images obtained in a patient with CAPS. The coapting surfaces of the mitral valve are studded with clusters of vegetations. (A) Short-axis view in diastole. (B) Short-axis view in systole. Reproduced with permission from Circulation.45

Table 2 Distinguishing echocardiographic features of IE and APS12,17,20-29,35-39

<table>
<thead>
<tr>
<th>Echocardiographic feature</th>
<th>IE</th>
<th>APS</th>
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<tbody>
<tr>
<td>Vegetation mobility</td>
<td>Mobile (pedunculated)</td>
<td>Mobile or immobile (broad based)</td>
</tr>
<tr>
<td>Tissue destruction</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Vegetation location</td>
<td>Usually near leaflet free margins</td>
<td>Base to mid (especially SAPS) or free margin (especially PAPS)</td>
</tr>
<tr>
<td>Mitral valve surface</td>
<td>Atrial</td>
<td>Atrial; occasionally ventricular</td>
</tr>
<tr>
<td>Aortic valve surface</td>
<td>Ventricular</td>
<td>Ventricular or vascular</td>
</tr>
<tr>
<td>Lesion number</td>
<td>Vegetations usually solitary</td>
<td>Single or multiple (eg, kissing vegetations)</td>
</tr>
<tr>
<td>Echogenicity</td>
<td>Usually homogeneous</td>
<td>Usually heterogeneous</td>
</tr>
<tr>
<td>Leaflet thickening</td>
<td>Absent</td>
<td>Often present</td>
</tr>
</tbody>
</table>

REFERENCES


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Figure 6  Transmirtal pulsed-wave Doppler recording taken before (A) and after (B) thromboendarterectomy in a patient with pulmonary hypertension due to chronic thromboembolic disease. The peak E-wave velocity increased markedly, and the deceleration time decreased from 240 to 165 ms postoperatively. Reproduced with permission from *J Am Coll Cardiol.*