Antiphospholipid Antibodies
A Marker of Lupus Carditis?

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Cardiac pathology is common in patients with systemic lupus erythematos (SLE). The pathological involvement includes pericarditis with or without effusion; myocarditis or cardiomyopathy, sometimes with involvement of the conducting system; and myocardial infarction secondary to coronary arteritis, or, more often, atherosclerosis. Left ventricular hypertrophy and left atrial dilatation often occur in response to renal hypertension.

Endocardial involvement in SLE is of particular interest because its recognized complications include thromboembolism, infective endocarditis, and the need for cardiac surgery. Since the original description by Libman and Sacks in 1924 of “a hitherto undescribed form of valvular and mural endocarditis,” there have been many reports of valve lesions occurring in patients with SLE. Verrucous endocardial lesions are ovoid, usually less than 4 mm in diameter, and consist of lymphocytes, plasma cells, and fibrous tissue as well as fibrin and platelet deposits. The lesions may be isolated or occur as a conglomerate of mulberrylike clusters at the edge of valves, most frequently affecting the mitral valve. Often, these valve lesions produce no symptoms, cause no murmurs of regurgitation or stenosis, and have no hemodynamic significance. However, more extensive lesions resulting in clinical and hemodynamic dysfunction are more frequent than previously recognized and may eventually necessitate valve replacement or repair.

Echocardiography

The most common clinical presentation of cardiovascular disease in patients with SLE is pericarditis. However, because pericarditis frequently occurs without effusion or pericardial thickening, the echocardiogram often fails to disclose evidence of pericardial disease, even when classic auscultatory findings are present. While vegetations of Libman-Sacks endo-

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Antiphospholipid Antibodies

The sera of patients with SLE contain many antibodies that react with native or altered autologous antigens; these include antibodies to nuclear components; antibodies to cell surface and cytoplasmic antigens of lymphocytes, polymorphonuclear cells, red blood cells, platelets, and neuronal cells; and antibodies to IgG and IgM. It is uncertain whether any of these autoantibodies are pathogenic per se or whether they merely serve as “markers” or “epiphenomena” to not-yet-elaborated basic immunologic abnormalities in particular subsets of SLE patients. An antigen-antibody reaction likely to affect the cardiac conduction system is suggested by the finding of ribonucleoprotein antibodies in both the sera of mothers with SLE and their affected infants with congenital complete atrioventricular block.

A recently defined group of antiphospholipid antibodies are found in increased serum concentrations in many patients with SLE, including the lupus “anticoagulant,” antibodies to IgG and IgM cardioprotein, and the false-positive test (VDRL) for syphilis. The antiphospholipid syndrome includes venous and arterial thromboses, recurrent spontaneous abortion, thrombocytopenia, livedo reticularis, and labile hypertension. While occurring most often in patients with SLE, the clinical complex also occurs in “non-lupus” patients who have some features of connective tissue disease and in patients with a “primary” antiphospholipid syndrome.
Correlation of Echocardiographic and Antibody Studies

In this issue of Circulation, Nihoyannopoulos and colleagues report their prospective two-dimensional echocardiographic studies in 51 patients with SLE who had elevated serum levels of antiphospholipid antibodies, in 42 patients with SLE but no raised levels of antiphospholipid antibodies, and in 12 patients with antiphospholipid antibodies who did not meet American Rheumatism Association classification criteria for SLE. Doppler echocardiography and color flow imaging were used as part of the echocardiographic assessment of each patient. Of 93 patients with SLE, 54% had abnormal echocardiographic findings. Valvular involvement occurred in 28% of the patients, and 21% had pericardial effusion or thickening. Five percent of the patients had regional or diffuse myocardial dysfunction. Evidence of pericardial disease was found in only a small portion of patients who had had one or more clinical episodes of pericarditis. Twenty-six percent of patients with SLE but no raised levels of antiphospholipid antibodies had echocardiographic evidence of cardiac disease compared with 78% of those with SLE and elevated serum levels of antiphospholipid antibodies. Of importance, the incidence of valvular heart disease (14% versus 40%) was greater in those with antiphospholipid antibodies. Also, the patients with high antiphospholipid antibodies titers had more severe valvular involvement, including verrucous lesions and valvular regurgitation or stenosis, than did patients with no increased antiphospholipid antibodies who had primarily localized valvular thickening with mild valvular regurgitation. Of interest, eight of the 12 patients with antiphospholipid antibodies but whose disease did not fulfill strict criteria for SLE had cardiac abnormalities that were similar in severity to those in patients with SLE and elevated antiphospholipid antibodies. These findings differ from those of a recent study of 70 patients with “primary” antiphospholipid syndrome in whom only two exhibited valvular lesions.

Several studies support the observation that SLE patients with antiphospholipid antibodies have a significantly higher frequency of valvular lesions than those without the antibodies. Recently, Galve and associates reported an 89% positivity for antiphospholipid antibodies in SLE patients with valve lesions determined echocardiographically compared with a 44% incidence in those without valvular involvement.

Tenable Hypotheses

Whether the antiphospholipid syndrome results in endocardial damage analogous to the endothelial damage invoked to explain the venous and arterial thromboses remains unanswered. Antiphospholipid antibodies may produce endothelial injury directly, leading to activation of clotting factors, platelet consumption, and thrombus formation. On the other hand, these antibodies might disrupt the normal coagulation cascade by interfering with phospholipid surface interactions among endothelial cells, platelets, and circulating proteins. An altered interaction of these components on the endocardial surface may result in a severe form of Libman-Sacks endocarditis. The previously quoted report suggesting that the “lupus process” itself is responsible for the basic valvular pathology is still consistent with a deleterious effect of the antiphospholipid antibodies. The antiphospholipid antibodies may result in superimposed thrombosis occurring on damaged or abnormally thickened valves in SLE patients. Thromboembolic complications, particularly involving the brain, have been associated with these antibodies as has obstruction of native valves or prosthetic replacements. Galve et al were unable to demonstrate a definite worsening of echocardiographic evidence of valvular disease in SLE patients during a follow-up period averaging less than 5 years.

Clinical Considerations

In view of this echocardiographic study and similar studies by other investigators, several important questions arise. First, which patients with SLE or the antiphospholipid antibody syndrome, but no cardiac symptoms, should undergo two-dimensional and Doppler echocardiography? Probably all. Second, which patients undergoing dental or surgical procedures should be treated with infective endocarditis antibiotic prophylaxis? Probably all with clinical or echocardiographic evidence of valvular heart disease. Third, should patients with verrucous vegetations on echocardiography be treated with anticoagulant therapy? Probably not, on the basis of a relatively low incidence of emboli. Fourth, do valvular lesions due to SLE and the antiphospholipid antibody syndrome develop or worsen on serial echocardiographic studies? This is not yet proven by serial echocardiographic studies, although the duration of follow-up has been relatively short. Finally, does steroid therapy have favorable or adverse effects on valvular lesions due to SLE, and how is this influenced by the presence of the antiphospholipid antibody syndrome? Many of these questions should be answered by further prospective studies concerning the cardiovascular manifestations of SLE and the results of serial echocardiographic and Doppler studies in such patients.

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