CME CREDIT

KATHLEEN MAKSIMOWICZ-McKINNON, DO
Department of Rheumatology, University of Pittsburgh Medical Center, Pittsburgh, PA

BRIAN F. MANDELL, MD, PhD
Department of Rheumatic and Immunologic Diseases, Vice-Chairman of Medicine for Education, The Cleveland Clinic Foundation; Deputy Editor, *Cleveland Clinic Journal of Medicine*

Understanding valvular heart disease in patients with systemic autoimmune diseases

ABSTRACT

Specific systemic autoimmune diseases are associated with distict valvular heart disorders. We discuss the valvular disorders associated with rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid antibody syndrome, the seronegative spondyloarthropathies, the systemic vasculitides, and scleroderma.

KEY POINTS

Valvular dysfunction is often asymptomatic, but may cause significant morbidity or death if undetected and untreated.

The surgical and medical therapy of valvular heart disease in patients with autoimmune diseases is dictated by the same hemodynamic indications as in the general population.

New or rapidly progressive valvular disease in any disorder may be the result of superimposed bacterial endocarditis. Infectious etiologies must be considered as part of the initial assessment.

Physicians should regularly screen for valvular involvement by history, focused physical examination, and, in certain conditions, by echocardiography.

SYSTEMIC AUTOIMMUNE DISEASES are often complicated by structural or functional valvular abnormalities or involvement of the pericardium, myocardium, and coronary arteries (vasculitis and premature coronary artery disease).

Physicians who are aware of the valvular disorders associated with specific autoimmune diseases (**TABLE 1**) may detect and start to manage them sooner, and possibly prevent some of the morbidity and death that these disorders can cause.

RHEUMATOID ARTHRITIS

Echocardiographic and autopsy studies reveal valvular abnormalities in up to 70% of patients with rheumatoid arthritis, although far fewer patients have symptoms.[1] These changes have been described as "nonspecific endocarditis," with valvular inflammation and fibrosis, and with thickening and calcific changes detected most commonly at the base of the valve and in the valve ring. These changes most frequently result in mild valvular insufficiency with minimal or no hemodynamic compromise.

Most of these patients have single valve involvement, but any or all valves may be affected. The mitral valve is most frequently affected, followed by the aortic, tricuspid, and pulmonic valves, in descending order of involvement.

Rheumatoid granulomata

The valvular lesions most distinctive of rheumatoid arthritis are rheumatoid granulo-

TABLE 1

Valvular involvement in autoimmune disorders

Rheumatoid arthritis
- Valvular insufficiency (mitral and aortic most common)
- Valvular stenosis (rare)
- May occur with or without rheumatoid granulomata

Systemic lupus erythematosus
- Valvular regurgitation or stenosis (most commonly mitral or aortic)
- Libman-Sacks endocarditis
- Inflammatory valvulitis
- Increased susceptibility to bacterial endocarditis and embolization

Antiphospholipid antibody syndrome
- Valvular regurgitation or stenosis
- Valvular thickening
- Thrombotic valvular vegetations with embolization

Seronegative spondyloarthropathies
- Aortic or mitral insufficiency
- Aortic root dilatation

Systemic vasculitis
- Aortic regurgitation (resulting from aortitis)
- Mitral, tricuspid regurgitation (infrequent in most, common in Kawasaki disease)

Scleroderma
- Valvular regurgitation (frequently tricuspid)
- Thickening of mitral and aortic valves

mata, which are found in 3% to 5% of patients at autopsy,[2] and which can be considered analogous to rheumatoid nodules. The granulomata may affect leaflet closure and lead to valvular incompetence or, less commonly, valvular stenosis.

Although conflicting data exist, some disease manifestations may predict valvular heart disease in rheumatoid arthritis. One study detected a significantly higher number of echocardiographic abnormalities in patients with more severe nodular rheumatoid arthritis (40%) than with non-nodular rheumatoid arthritis (17.2%) or in controls (14.3%).[3]

Valvular disease associated with rheumatoid arthritis is most often clinically quiescent, but a few patients develop rapid, progressive valvular incompetence. Some valve granulomata regress with steroid therapy, with associated hemodynamic improvement. Nodular valve lesions may be a nidus for thrombus or infection.

Given the infrequency of clinically significant valve dysfunction, there are no specific recommendations for screening or treatment for valvular abnormalities in rheumatoid arthritis.

Aortitis

Aortitis with associated hemodynamic compromise may occur in rheumatoid arthritis, but is rarely diagnosed antemortem. An autopsy series of 188 rheumatoid arthritis patients identified 10 patients with aortitis, most of them seropositive with nodular disease.[4] This suggests that this complication may be more common than previously thought, especially in this subset of patients.

Although routine screening for this manifestation is unnecessary, a thorough history and examination addressing signs and symptoms of cardiovascular disease is an important part of the routine health care of patients with rheumatoid arthritis.

The impact of more aggressive early treatment and the new biologic therapies for rheumatoid arthritis on the development and progression of valvular disease and aortitis is unknown.

SYSTEMIC LUPUS ERYTHEMATOSUS

Valvular abnormalities can be found on echocardiography in up to 54% of patients with systemic lupus erythematosus (SLE).[5] Most common is nonspecific thickening of the mitral and aortic valves. Owing to this thickening, the valve cusps may not close properly, and approximately 2% to 8% of patients with valvular incompetence require surgery for hemodynamically significant regurgitation.[6,7]

The most characteristic valvular abnormality of SLE is Libman-Sacks endocarditis: noninfectious verrucous valvular vegetations, most commonly on the mitral valve but often on multiple valves. The verrucae are most often found in the recess between the ventricle wall and posterior valve leaflet, but can involve either surface of the valve, the commissures, and the rings, and less commonly the chordae, papillary muscles, and endocardium. Their histopathologic appearance may vary, with hematoxylin bodies, immunoglobulin

deposits, fibrin, and granular materials detected in pathologic specimens.

Although fewer cases of Libman-Sacks endocarditis are detected at autopsy now that corticosteroids are commonly used to treat many aspects of SLE, some data indicate that healing of verrucous lesions results in scarring and shortening of leaflets, with valvular insufficiency. Valvular disease in SLE may occur or progress independently of systemic disease activity or severity.

Of note: about 50% of patients with a history of cardiovascular disease and SLE have valvular dysfunction, which is significantly less common in patients without known cardiovascular disease.[8]

Pulmonary hypertension may occur in SLE. The mechanism is still unclear, but suspected mechanisms include valvular disease, thrombosis, embolism, pulmonary fibrosis, and pulmonary vasculitis.[9]

A caveat: although there is no specific treatment for valvular heart disease in SLE, Libman-Sacks endocarditis is a pathologic diagnosis and should clinically be a diagnosis of exclusion. Other diseases, such as infective endocarditis or antiphospholipid antibody syndrome, which also are associated with valvular lesions in SLE and merit other treatments, should be considered before this diagnosis is made. It may not always be possible to distinguish between the antiphospholipid antibody syndrome and valvular disease associated with SLE in the presence of antiphospholipid antibodies.

Bacterial endocarditis prophylaxis should be considered for SLE patients with valvular heart disease, following American Heart Association guidelines. There is no consensus on antibiotic prophylaxis in patients with SLE without known valvular disease. However, because valvular heart disease is common in patients with SLE, some authors have suggested that all SLE patients undergoing procedures associated with transient bacteremia should be considered for antibiotic prophylaxis.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Antiphospholipid antibodies are directed against protein-phospholipid complexes and are frequently associated with a thrombotic state. The syndrome can be primary (an isolated disorder) or secondary (part of another disorder such as SLE).

Both primary and secondary antiphospholipid antibody syndrome are associated with an increased prevalence of cardiovascular abnormalities, eg, nonspecific thickening of valve leaflets, thrombotic valvular vegetations, free-floating thrombi, and valvular insufficiency.

Thromboembolic disease may lead to clinically significant pulmonary hypertension. Valvular abnormalities in antiphospholipid antibody syndrome may resolve spontaneously or progress. Hemodynamically significant valvular insufficiency requiring surgical intervention is uncommon. Free-floating or valve-associated thrombi may resolve with long-term anticoagulation.

The mechanisms of antiphospholipid antibody-associated valvular dysfunction are unknown, but several have been suggested. Immune complexes may injure the valvular endothelium; the phospholipid interaction between endothelial cells and platelets may be disrupted; or the capillaries within the valvular endothelium may be damaged. Any of these processes may lead to subsequent thrombotic and fibrotic changes of the valve. Data exist to both support and refute a relationship between antiphospholipid antibody titers and valvular disease, leaving this association unclear. Titers of antiphospholipid antibodies may fluctuate or even become transiently negative in the antiphospholipid antibody syndrome and have no direct role in the diagnosis or monitoring of antiphospholipid-associated valvular heart disease.

Antiphospholipid antibody titers have no role in diagnosing or monitoring valve disease

Patients with the antiphospholipid antibody syndrome, by definition, have had thrombotic events or recurrent spontaneous abortions. Patients with a history of arterial or venous thrombosis generally require chronic anticoagulation therapy.

Patients with SLE who have persistent antiphospholipid antibodies (measured in the same laboratory at least twice, at least 6 weeks apart) without the clinical syndrome do not require treatment, but often are given low-dose aspirin (81 mg/day). No data as yet have demonstrated a benefit to this approach,

despite an appropriate rationale.

Patients with valvular heart disease and antiphospholipid antibodies should be given bacterial endocarditis prophylaxis prior to procedures associated with transient bacteremia.

SERONEGATIVE SPONDYLOARTHOPATHIES

The seronegative spondyloarthropathies include ankylosing spondylitis, psoriatic arthritis, and Reiter syndrome.

Cardiac involvement has been best studied in ankylosing spondylitis, in which aortic root or left-sided valvular insufficiency is noted in up to 100% of cases in autopsy series. Echocardiographic studies in patients with ankylosing spondylitis demonstrate an increased prevalence of aortic valve and root disease in patients (82%) compared with controls (27%) matched for age and sex.[10]

Three factors may contribute to aortic valvular dysfunction in ankylosing spondylitis: aortic root dilation, valvular fibrosis with retraction of the cusp bases, and inward rolling of the cusp margins.[11] Additionally, mitral insufficiency may occur as a result of subaortic fibrosis of the anterior valve leaflet. This anatomic defect may be seen as a "subaortic hump" or ridge on echocardiography. Histopathology of the valvular lesions demonstrates inflammation of the aortic root with obliterative endarteritis and fibrosis.

Up to 50% of patients with ankylosing spondylitis have valve insufficiency

The prevalence of valvular insufficiency has been reported in up to 50% of patients with ankylosing spondylitis, and appears to be related to disease duration.

Spondyloarthropathy-associated valvular dysfunction can resolve or progress over time. Roldan et al followed 25 patients over 3 years with serial echocardiography and found new valvular abnormalities in 6 (24%), worsening of prior abnormalities in 3 (12%), and, surprisingly, resolution of abnormalities in 5 (20%).[10] In addition, 5 (20%) developed congestive heart failure, had a cerebrovascular accident, required valve replacement, or died of other cardiovascular causes.

Patients with spondyloarthropathy, especially when HLA-B27-positive, have an increased incidence of conduction system abnormalities, which may result in bradyarrhythmias or heart block. These may be due to fibrotic changes affecting the atrioventricular node or septum. In a patient without symptoms, a routine history and a focused cardiovascular examination with occasional electrocardiograms are adequate for screening.

Although there are no specific treatment recommendations for asymptomatic valvular abnormalities associated with spondyloarthropathy, careful surveillance with periodic inquiries for the development of cardiovascular symptoms and a thorough examination is appropriate, with imaging indicated at time of recognition. All patients with spondyloarthropathy or an HLA-B27-associated syndrome should be considered at increased risk for all of the above complications.

Patients with valvular lesions should be given bacterial endocarditis prophylaxis with the same stipulations as in the general population with similar valve lesions.

SYSTEMIC VASCULITIS

Many of the vasculitides have been associated with valvular heart disease. Aortitis with associated aortic insufficiency has been documented in giant cell arteritis, Takayasu arteritis, Wegener granulomatosis, sarcoidosis, Behçet syndrome, and relapsing polychondritis.[12–18] Insufficiency of other heart valves may occur in these disorders as a result of valvulitis, but this is rare.

Kawasaki disease is most often associated with coronary arteritis and pancarditis, but may be complicated by valvular dysfunction, usually resulting from myocarditis or acute valvulitis. One study demonstrated mitral regurgitation in up to 47% of patients and tricuspid regurgitation in up to 53% during the acute phase of the disease.[18]

In many vasculitis patients, the valvular lesions resolve after the disease goes into remission; even if valvular disease persists, it rarely progresses to significant stenosis. Aortitis may be initially recognized at the time of surgery for aortic valve dysfunction or repair of a thoracic aortic aneurysm.

Treatment of the underlying disorder is the therapy of choice for aortitis or valvulitis associated with systemic vasculitis. Not uncommonly, aortic valve replacement for

insufficiency in this setting requires repair of the aorta, often with graft placement.

Unfortunately, follow-up of aortitis is often not straightforward; neither serologic or acute-phase reactant monitoring nor sequential imaging is completely reliable to detect recurrent or ongoing inflammation. If elevation of acute phase reactants is associated with aortitis preoperatively, this may be useful to follow, with the caveat that normal levels of acute phase reactants do not exclude active progressive vascular inflammation. Serial imaging by magnetic resonance angiography with edema-weighted images may be helpful in detecting wall thickening or "edema," but these findings do not always indicate active inflammation.[19] Conversely, inflammation can exist or progress without visible changes on imaging.

Detection and monitoring of aortitis remains a challenge. Once aortitis is detected, regular screening for development of aortic aneurysm or aortic branch stenoses should be performed by repeated focused physical examinations and occasional imaging. Since stenotic lesions are often close to the takeoff from the aorta, magnetic resonance angiography is frequently utilized instead of angiography.

SCLERODERMA

Symptomatic valvular heart disease in patients with scleroderma is uncommon, but valvular insufficiency has been documented by echocardiography. This most frequently results from nonvalvular hemodynamic alterations, such as pulmonary hypertension or ventricular hypertrophy and fibrosis.[20] The finding of tricuspid insufficiency in a patient with scleroderma should raise suspicion for underlying pulmonary hypertension and mandate appropriate evaluation and therapy.

Follow-up of aortitis is not always straightforward

REFERENCES

1. **Kitas G, Banks M, Bacon P.** Cardiac involvement in rheumatoid disease. Clin Med 2001; 1:18–21.
2. **Carpenter DF, Golden A, Roberts WC.** Quadrivalvular rheumatoid heart disease associated with left bundle branch block. Am J Med 1967; 43:922–929.
3. **Wislowska M, Sypula S, Kowalik I.** Echocardiographic findings and 24-h electrocardiographic Holter monitoring in patients with nodular and non-nodular rheumatoid arthritis. Rheumatol Int 1999; 18:163–169.
4. **Gravallese EM, Corson JM, Coblyn JS, Pinkus GS, Weinblatt ME.** Rheumatoid aortitis: a rarely recognized but clinically significant entity. Medicine 1989; 68:95–106.
5. **Nihoyannopoulos P, Gomez PM, Joshi J, Walport MJ, Oakley CM.** Cardiac abnormalities in systemic lupus erythematosus. Circulation 1999; 82:369–375.
6. **Moder K, Miller T, Tazelaar H.** Cardiac involvement in systemic lupus erythematosus. Mayo Clin Proc 1999; 74:275–284.
7. **Galve E, Candell-Riera J, Pigrau C, et al.** Prevalence, morphologic types and evolution of cardiac valvular disease in systemic lupus erythematosus. N Engl J Med 1988; 319:817–823.
8. **Jensen-Urstad K, Svenungsson E, de Faire U, et al.** Cardiac valvular abnormalities are frequent in systemic lupus erythematosus patients with manifest arterial disease. Lupus 2002; 11:744–752.
9. **Tanaka E, Harigai M, Tanaka M, Kawaguchi Y, Hara M, Kamatani N.** Pulmonary hypertension in systemic lupus erythematosus: evaluation of clinical characteristics and response to immunosuppressive treatment. J Rheumatol 2002; 29:282–287.
10. **Roldan C, Chavez J, Wiest P, Qualls C, Crawford M.** Aortic root disease and valve disease associated with ankylosing spondylitis. J Am Coll Cardiol 1998; 32:1397–1404.
11. **Bergfeld L.** HLA-B27-associated cardiac disease. Ann Intern Med 1997; 127:621–629.
12. **Nesi G, Anichini C, Pedemonte E, et al.** Giant cell arteritis presenting with annuloaortic ectasia. Chest 2002; 121:1365–1367.
13. **Deyu Z, Guozhang L.** Clinical study of aortic regurgitation in patients with aortoarteritis. Int J Cardiol 2000; 75:S141–S145.
14. **Leff R, Hellman R, Mullany C.** Acute aortic insufficiency associated with Wegener granulomatosis. Mayo Clin Proc 1999; 74:897–899.
15. **Weiler V, Redtenbacher S, Bancher C, Fischer MB, Smolen JS.** Concurrence of sarcoidosis and aortitis: case report and review of the literature. Ann Rheum Dis 2000; 59:850–853.
16. **Ando M, Okita Y, Sasako Y, Kobayashi J, Tagusari O, Kitamura S.** Surgery for aortic regurgitation caused by Behcet's disease: a clinical study of 11 patients. J Card Surg 1999; 14:116–121.
17. **Selim AGA, Fulford LG, Mohiaddin RH, Sheppard MN.** Active aortitis in relapsing polychondritis. J Clin Pathol 2001; 54:890–892.
18. **Suzuki A, Kamiya T, Tsuchiya K, et al.** Tricuspid and mitral regurgitation detected by color flow Doppler in acute phase of Kawasaki disease. Am J Cardiol 1988; 61:386–390.
19. **Tso E, Flamm SD, Whit RD, Schvartzman PR, Mascha E, Hoffman GS.** Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum 2002; 46:1634–1642.
20. **Battle R, Davitt M, Cooper S, et al.** Prevalence of pulmonary hypertension in limited and diffuse scleroderma. Chest 1996; 110:1515–1519.

ADDRESS: *Brian F. Mandell, MD, PhD, Vice-Chairman of Medicine for Education, NA20, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; email mandelb@ccf.org.*