Cardiac Valve Involvement in Systemic Diseases: A Review

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ABSTRACT

Increasing age and new trends of mixed populations have newly aroused interest in valvular heart disease in the developed countries still in need of new clinical insights. In the clinical setting of systemic diseases, the proper assessment of cardiovascular abnormalities may be challenging, and the characterization of valvular involvement might help to recognize the underlying disease and cardiac sequelae. Prompt identification of valvular lesions may, therefore, also be useful for differential diagnosis. This article reviews the cardiac involvement in systemic diseases from etiology and background definition to echocardiographic assessment and clinical interpretation.

Introduction

In several systemic diseases, valvular involvement is 1 of the most prevalent and important forms of cardiac abnormalities. Echocardiography plays a valuable role in the assessment and clinical decision making of morphological and functional valvular abnormalities. In this review we evaluated the valvular involvement in several systemic diseases, all sharing a possible involvement of heart valves.

Connective Tissue Disease

Systemic Lupus Erythematosus and Antiphospholipid Syndrome

Several cross-sectional and prospective studies indicated that patients with systemic lupus erythematosus (SLE) have an increased prevalence of cardiovascular disease. An association was described between these cardiovascular disorders and antiphospholipid antibodies either in patients with SLE or in subjects with so-called primary antiphospholipid syndrome (APS). In a recent meta-analysis, a 3-fold higher risk for any valve lesion in SLE patients with antiphospholipid antibodies was demonstrated for the first time.

Inflammatory as well as thrombotic mechanisms are thought to be responsible for cardiac valve disease in APS.^{1–2}

More than one-half of SLE patients probably have abnormal valves. Two morphological echocardiographic patterns can be discerned: Libman-Sacks (L-S) vegetations, found in approximately 1/10 patients with SLE, and valvular thickening, which is much more common. The predominant functional abnormality is regurgitation. The mitral valve (MV) is mainly affected, followed by the aortic valve (AV).³ The degree of anatomical and functional abnormality is usually mild to moderate and clinically silent. Infrequently, even mild disease may be complicated by cardioembolism and hemodynamically significant regurgitation due to acute immune-mediated valvulitis or infective endocarditis.⁴

Echocardiographically, L-S vegetations appear as valve masses of varying size (usually <1 cm) and with irregular borders and echo density, firmly attached to the valve surface, or exhibiting an independent motion similar to thrombi. Whereas in previous postmortem studies where vegetations were seen mostly near the valve tips, other echocardiographic data showed their predominant location to be on the proximal or middle portion of the leaflets or cusps (on the atrial side of the MV and the aortic side of the aortic cusps). Vegetations may extend to the subvalvular apparatus and the adjacent mural

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endocardium. The leaflet fibrosis (ie, increased thickness >3 mm and echocardiographic reflectance) accompanying L-S vegetations may cause reduced leaflet mobility, but valve stenosis is rare (<3%).

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an articular inflammatory disease of unknown etiology, with a worldwide prevalence of about 1%. Cardiac involvement is common and occurs in up to 50% of the affected patients.⁵ Guedes et al⁶ showed an increased incidence of mitral, aortic, and tricuspid valve dysfunction, involving up to 83% of RA patients. RA valve disease is almost always mild and asymptomatic, and is less likely than SLE to result in clinically significant valve dysfunction. According to the major pressure load faced by the valves, the MV is most commonly injured in RA, and it is followed in frequency by the aortic, tricuspid, and pulmonary valves.

The main alteration is leaflet thickening and valve granulomas.⁷ The leaflet fibrosis is indistinguishable from that seen in SLE. In contrast, valve granulomas appear to be unique to RA (histologically resembling subcutaneous rheumatoid nodules). Rheumatoid valve nodules usually appear as small (<0.5 cm²) spheroid masses with homogeneous reflectance, usually appearing singly and on any portion of the leaflet. The adjacent leaflet appears normal or shows mild sclerosis. This picture is unlike that of L-S vegetations. These granulomas can also be seen on valve rings, papillary muscle tips, and atrial or ventricular endocardium.

Systemic Sclerosis

Systemic sclerosis (SSc) is a connective tissue disease characterized by widespread vascular lesions and fibrosis of the skin and internal organs. Cardiac involvement is often clinically occult, but it is recognized as a poor prognostic factor.⁸ Published data suggest that scleroderma rarely causes valve disease. Small masses similar to L-S

vegetations, aortitis, aortic regurgitation (AR), and an increased frequency of MV prolapse (MVP) were reported.⁹

Seronegative Arthritis

HLA-B27, an immunogenetic marker present in 8% of the white population, has been found to be an important risk factor for the development of a group of rheumatic disorders—the seronegative spondyloarthropathies (Reiter's syndrome and ankylosing spondylitis [AnSp])—which were found to be the probable underlying cause in 15% to 20% of patients with lone AR.¹⁰

The presence of aortic root and valve disease in AnSp is related to the duration of the underlying disease and is caused by an inflammatory process coupled with platelet aggregation, leading to endarteritis and fibroblast hyperactivity and consequent tissue thickening involving aortic annulus, cusps, aorto-mitral junction, along with the conduction system.¹¹ The abnormal thickening of the valvular cusps (Figure 1, left), the dilatation of the aortic root, and the abnormal cusps displacement via the thickened subaortic tissue all lead to generally mild to moderate AR (Figure 1, right). Aortic root and valve disease were found in 82% of patients (vs 27% in controls). AR is most commonly seen in patients with AnSp; however, mitral regurgitation (MR) is also known to occur. The proposed mechanism is basically a continuation of the fibrosis of the subaortic tissues, which can progress to reach the anterior mitral leaflet. This often results in localized fibrotic thickening at the base of the anterior mitral leaflet, a condition called subaortic bump.

Marfan Syndrome

Marfan syndrome (MaSy) is an autosomal dominantly inherited disease of the connective tissue caused by mutations in the gene coding for fibrillin-1. The life expectancy of untreated patients is markedly short, mainly because of cardiovascular complications such as aortic rupture and MV dysfunction.

Figure 1. Aortic valve involvement in ankylosing spondylitis. Transesophageal echocardiography: the aortic cusps appear abnormally thickened (left) and displaced leading to severe insufficiency (right). Abbreviations: Ao, aorta; LV, left ventricle.

Figure 2. Barlow's disease in Marfan syndrome. Three-dimensional echocardiography showing an en face view of large bi-leaflet mitral valve prolapse.

Annuloaortic ectasia, especially with dilatation of the aortic root, is found in 60% to 80% of adults with MaSy. It usually begins with dilation of the aortic sinuses, which progresses into the sinotubular junction and ultimately into the aortic annulus. Dilation of the aortic root is the leading cause of AV insufficiency in MaSy. In annuloaortic ectasia, severe AR occurs and may progress to aortic root dissection or rupture.¹² On mid-systolic images, the cusps of the AV appear tethered instead of demonstrating their normal arching appearance; the tethered appearance results from the dilation of the Valsalva sinus. On end-diastolic images, valvular insufficiency is depicted as a triangular coaptation defect.

Aortic aneurysm without annuloaortic ectasia is also common. Compared with atherosclerotic aneurysms, aortic aneurysms in MaSy commonly occur in younger patients and enlarge more rapidly.

Another distinctive pattern of MaSy is represented by MVP, which is less benign than the common type of MVP identified in the general population. In contrast to idiopathic MVP, for which the average age was 65 years and the frequency of MVP-related events was 13%, Rybczynski et al¹³ found that patients with MaSy experienced clinical events almost 30 years earlier and at a frequency more than twice. Flail leaflet was an independent predictor of progression of MR and MV-related clinical events. Moreover, 50% of patients with MaSy exhibit a nonclassic pattern¹⁴ or bi-leaflet valve involvement (Figure 2), which differs from diagnostic criteria for classic MVP.

Ehlers-Danlos Syndrome/Osteogenesis Imperfecta/Pseudoxanthoma Elasticum

Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum are rare inheritable disorders of the connective tissue. Aortic root dilation is the most common cardiovascular manifestation. Left-sided heart valves are preferentially affected, leading to AR and MR.

In some cases, echocardiography demonstrated marked MVP of the both leaflets and vegetation-like thickening of the anterior leaflet of the MV. Only 1 case was reported with right-sided cardiac involvement in osteogenesis imperfecta.^{15–17}

Vasculitides

Antineutrophil Cytoplasmic Antibodies Disease

Antineutrophil cytoplasmic antibodies (ANCA) diseases, a group of small vessel vasculitic syndromes, include Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome.¹⁸ Lacoste et al¹⁹ reviewed 20 cases consistent with a systemic ANCA-associated vasculitis with endocardial valvular involvement; the most commonly valvular lesion was AR. Seven cases of MR and 1 of aortic stenosis, 2 cases of valvular vegetations, and 2 of a mass involving a mitral leaflet responsible for mild mitral stenosis and moderate MR were also reported. Six patients had polyvalvular involvement.²⁰

Several mechanisms responsible for these valvular lesions have been reported: vegetations, leaflet thickening, valvular perforation, and unique or multiple endocardial masses. Half of the valvular lesions were present at the time of diagnosis.

Behcet's Disease

Behcet's disease (BD) most often leads to aortitis involving the aortic root, with AV leaflet destruction and AR necessitating AV replacement. MV involvement is even more rare including MVP and MR. AV or MV vegetations are rarely seen, and this echocardiographic feature may be useful in differentiating BD from infective endocarditis.²¹

Polyarteritis Nodosa

Polyarteritis nodosa is a necrotizing vasculitis of small and medium-sized muscular arteries. Reported rates of cardiac manifestations range from 0% to 86%. Mitral and/or tricuspid regurgitation are the most prominent echocardiographic findings detected.²²

Takayasu Arteritis

The most common presentation of Takayasu arteritis (TA) includes symptoms resulting from arterial occlusive disease of the aorta, aortic arch, and large vessels, with a predilection for young women. Nearly 40% of patients with TA develop cardiac abnormalities, including acute aortic insufficiency.²³ The cardiac pathology is directly related to the aortic inflammation, including AR as a result of aortic root dilation, which may occur in 20% of cases, and coronary ostial stenoses resulting from aortitis. Echocardiography plays a key role in the assessment of the aortic root and AV in the setting of aortitis of the ascending thoracic aorta associated with AR and aneurysm formation.²⁴

Neoplastic Disease

Carcinoid Heart Disease

Carcinoid tumors are rare neuroendocrine malignancies. In more than 50% of patients with carcinoid syndrome, carcinoid heart disease develops. Carcinoid heart disease

Figure 3. Tricuspid valve involvement in carcinoid heart disease. At echocardiography, the tricuspid valve leaflets appear thickened, shortened, and displaced (A), resulting in severe valvular regurgitation (B). Abbreviations: LA, left atrium; RA, right atrium; RV, right ventricle.

is characterized by plaques of fibrous tissue related to vasoactive substances delivered by the carcinoid tumor. It is thought that high circulating serotonin concentrations are a major contributor to development of carcinoid heart disease.

The disease predominantly affects the right-sided valves as the lungs filter the tumor products before they reach the left atrium. If carcinoid valvular heart disease involves the MV or AV, a right-to-left shunt or a primary bronchial carcinoid is frequently found.²⁵

At echocardiography, the tricuspid valve leaflets are typically thickened and shortened (Figure 3A). With progression of the disease, the leaflets become increasingly retracted, resulting in reduced mobility. The septal and the anterior leaflets are predominantly affected, whereas the posterior leaflet may exhibit relatively preserved mobility. In advanced stages of tricuspid valve disease, the leaflets become fixed in a semiopen position, resulting in severe tricuspid regurgitation (Figure 3B) and some degree of concomitant stenosis due to a fixed orifice. The pulmonary valve cusps appear thickened with retraction and reduced mobility. The cusps may be difficult to visualize if severely retracted. Constriction of the pulmonary annulus as a result of plaque deposition may also be observed. Occurrence of hemodynamically relevant pulmonary valve stenosis is more frequently noted than tricuspid stenosis. Left-sided valvular involvement is infrequent; however, it is characterized by diffuse valve thickening and retraction with reduced mobility and regurgitation but without significant stenosis.²⁶

Marantic Endocarditis Associated With Cancer

Nonbacterial thrombotic endocarditis (NBTE), formerly known as marantic endocarditis, is characterized by the deposition of thrombi on previously undamaged heart valves in the absence of a bloodstream bacterial infection and by

increased rates of arterial embolic events in patients with chronic debilitating diseases. The most commonly affected valves (in descending frequency) are the AV, the MV, and a combination of both. Involvement of the right-sided heart valves has also been reported. Vegetations typically occur at the coapting edge of the leaflets and in general do not alter or impede valve function²⁷ (Figure 4). The masses vary in size from microscopic to large and exuberant, with a tendency to detach and cause embolism.

Infiltrative Cardiomyopathies

Amyloidosis

The term cardiac amyloidosis refers to heart involvement as a result of amyloid deposition in heart tissue. Classic signs of amyloidosis, such as increased thickness of the interventricular septum, both ventricles, and the interatrial septum are only characteristic of advanced phases of the disease. A granular pattern in the myocardium has been proposed as a typical sign of this disease entity. Diastolic dysfunction is the echocardiographic finding of this disease, and it is present in almost all patients. Strain rate imaging allows documenting cardiac disease in its early stages, as it detects impairment of longitudinal contractile function.

Amyloid deposition may cause cardiovascular dysfunction in a variety of ways, and several reports have described stenotic valvular lesions, although there are many patients with cardiac amyloidosis and mild or moderate MR. Only few cases described severe MR: 1 with extensive amyloid infiltration of the myocardium and papillary muscles, 1 with a ruptured chorda, and histological findings revealing amyloid deposits in both the MV and chordae.²⁸

Sarcoidosis

Sarcoidosis is a chronic multisystemic disorder of unknown etiology characterized by an accumulation of T lymphocytes

Figure 4. Marantic endocarditis of the aortic valve in a patient with hepatocellular carcinoma. At echocardiography, the nonbacterial thrombotic vegetations appear as soft masses strictly attached to the endocardial surface of the aortic cusps (A) without interfering with the valvular function. After orthotopic liver transplantation, the aortic valve masses disappeared (B). Abbreviations: Ao, aorta; LV, left ventricle.

and mononuclear phagocytes, noncaseating granulomas, and derangement of normal tissue architecture. Cardiac sarcoidosis has a variety of cardiac manifestations, including congestive heart failure due to cardiac involvement (the LV free wall is most commonly affected), but also may be the result of MV dysfunction secondary to papillary muscle infiltration or rupture.²⁹

Mucopolysaccharidosis

Cardiac involvement in mucopolysaccharidosis is common and has been reported in all forms.³⁰ Echocardiographic abnormalities in this storage disease have been reported, with patchy thickening of the valves. In Maroteaux-Lamy syndrome, a variant of Hurler syndrome, the MV is the most frequently involved, and insufficiency is the more common manifestation, although mitral stenosis (MS) is seen. Sheie syndrome, a forme fruste of Hurler disease, has been associated with mitral and AV involvement, either stenotic, insufficient, or both. Butman et al³¹ described a case of severely stenotic AV that was combined with MS for the first time.

Fabry Disease

Fabry disease (FD) is a rare X-linked recessive genetic disorder that leads to widespread and progressive disease caused by accumulation of glycosphingolipids in vascular endothelium and other tissues. Cardiac manifestations of FD include valvular dysfunction. Mild thickening of the AV and MV leaflets is seen in 25.5% of patients, and mild MVP is documented in 10.9% of patients.³² Mild MR and AR may be due to stiffening of the leaflets as a result of valvular infiltration by glycosphingolipids. Hypertrophy of papillary muscles and/or systolic anterior motion of the mitral leaflets associated with left ventricular (LV) outflow obstruction may aggravate the MV dysfunction.

Endomyocardial Fibrosis/Idiopathic Hypereosinophilic Syndrome

Endomyocardial fibrosis (EMF) is considered the most common form of restrictive cardiomyopathy. Diagnostic

criteria for the diagnosis of right EMF are represented by reduction of right inflow cavity/right ventricular cleavage plane between fibrous and myocardial tissue (Figure 5A,B), parietal thrombi, right atrial dilatation, fibrotic entrapment of tricuspidal leaflets in the endocardial wall leading to insufficiency (Figure 5B,C), inferior vena cava dilatation, and pleuropericardial effusions. Another EMF case, with prevalent left EMF, showed oval deformation of the LV cavity, apical endocardial calcification (Figure 5C), and extreme posterior mitral leaflet retraction/hypoplasia with insufficiency (Figure 5D).³³ Atrioventricular valve dysfunction is the result of repeated inflammatory episodes that lead to marked leaflet retraction. This process is a morphological and clinical determinant of the disease and is among the major diagnostic criteria described by Mocumbi et al.³⁴

The term idiopathic hypereosinophilic syndrome (IHS) describes a heterogeneous group of diseases characterized by unexplained hypereosinophilia and organ involvement in varying degrees. Löffler's endomyocarditis is used to describe the involvement of the heart in IHS and is considered the Western form of EMF, which is far more common at tropical latitudes. Endomyocardial thickening, apical obliteration due to thrombus formation, and posterior mitral leaflet involvement are classical findings as well.

Other Conditions

Chronic Kidney Disease

The 2 most common forms of cardiac valvular disease in chronic kidney disease (CKD) are AV calcification and sclerosis (28% to 31% of patients with end-stage renal disease) and mitral annular calcification (10% to 36% of patients on dialysis). The calcification may also occur in atypical areas such as the base of both mitral leaflets and intervalvular fibrosa. In both of these conditions, the uremic milieu of CKD, mineral and bone disorders promote accelerated calcification. Elevated phosphorus levels are the most potential pathogenic factor in CKD.³⁵ AV regurgitation is caused by calcification and occurs in 13% of CKD patients. MR may occur in 38% of renal failure patients and may be caused by mitral annular calcification or LV dilation.

Figure 5. Valvular involvement in Ugandan endomyocardial fibrosis (EMF). Echocardiography shows total (A) or partial (B) right ventricular obliteration by fibrous tissue (short arrows) and fibrotic entrapment of tricuspid leaflets in the endocardial wall, leading to insufficiency (B, D arrows) and pleuropericardial effusions (yellow markers). In the isolated LV EMF, apical endocardial calcifications may occur (C, arrowheads), together with severe retraction/hypoplasia of mitral posterior leaflet, leading to insufficiency (B, D arrows). Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Hyperparathyroidism

Hypercalcemia due to primary hyperparathyroidism may induce calcification of coronary arteries, myocardium, and valves. AV calcification occurs in 46% to 63% of primary hyperparathyroidism patients, and MV or submitral annulus calcification has been reported in 33% to 49% of these patients. Aortic and mitral stenosis may result from primary hyperparathyroidism.³⁶

Dyslipidemia

Active smoking and elevated total cholesterol levels are major risk factors for degenerative AV disease (DAVD) in the general population.³⁷ Interestingly, DAVD is often accompanied by degenerations of the MV, suggesting common pathogenetic mechanisms.

Drugs

Antiobesity drugs (fenfluramine, dexfenfluramine); ergot-derived dopamine agonists (pergolide, cabergoline) to treat Parkinson's disease, restless leg syndrome, and

hyperprolactinemic disorders; ergot alkaloid drugs including methysergide and ergotamine (for migraine headache); have all been linked to valvulopathy in humans.^{38–40} These valvular changes resemble lesions associated with carcinoid heart disease. Prevalence varies considerably between studies, ranging from 6% to 30%. The duration of treatment plays a role in the development of clinical valvulopathy.

Conclusion

There are a number of systemic diseases that may lead to cardiac valve involvement (Table 1). Anomalies detectable may be specific (vegetations for SLE/APS antibodies, SSc, NBTE, ANCA-associated vasculitis, or granulomas for RA) or aspecific (leaflet thickening for SLE/APS, ANCA-associated vasculitis, RA, seronegative spondyloarthritis, IHS, carcinoid, drugs; and calcifications for CKD, hyperparathyroidism, dyslipidemia). Occasionally, valvular disease may be associated with aortic root involvement (SSc, MaSy, Ehlers-Danlos, vasculitides, seronegative spondyloarthritis). The knowledge of these lesions may be also useful for differential diagnosis (ie, L-S vegetation from infective

Table 1. Cardiac Valve Involvement in Systemic Diseases

	Vegetations	MVP	Aortic Root Abnormalities	Leaflet Thickening	Infiltration
SLE/APLS	X			X	
SS	X		X		
NBTE	X				
ANCA-associated vasculitis	X			X	
RA				X	
Marfan syndrome		X	X		
Ehlers-Danlos		X	X		
Takayasu			X		
Behcet			X		
Osteogenesis imperfect		X	X		
Pseudoxanthoma elasticum		X	X		
Fabry disease		X			X
AS			X	X	
IHS				X	
Carcinoid				X	
Mucopolysaccharidosis					X
Sarcoidosis					X
Amyloidosis					X
Hyperparathyroidism					X
Renal disease					X
Dyslipidemia					X
Drugs				X	

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; APLS, antiphospholipid syndrome; AS, aortic stenosis; IHS, idiopathic hypereosinophilic syndrome; MVP, mitral valve prolapse; NBTE, nonbacterial thrombotic endocarditis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic sclerosis.

endocarditis). Echocardiography plays an important role in assessing the diagnosis and the extent of the lesions, the degree of cardiac sequelae (thromboembolic events, superadded infective endocarditis), and in the follow-up of residual damage possibly affecting the prognosis. Occasionally, the detection of subclinical valvular involvement may represent the first sign leading to the diagnosis of a previously unknown systemic disease.

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