Rev Port Cardiol. 2012;31(4):295–299

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

REVIEW ARTICLE

Valvular lesions in patients with systemic lupus erythematosus and antiphospholipid syndrome: An old disease but a persistent challenge

Ester Ferreira[c,a], **Paulo M. Bettencourt**[c,a], **Luís M. Moura**[b,a,*]

[a] *Department of Medicine, Oporto School of Medicine, University of Oporto, Portugal*
[b] *Pedro Hispano Hospital, Matosinhos, Portugal*
[c] *São João Hospital, Oporto, Portugal*

Received 4 July 2011; accepted 22 September 2011
Available online 3 March 2012

KEYWORDS
Lupus erythematosus systemic (LES);
Antiphospholipid syndrome (APS);
Valvular disease;
Treatment;
Complications;
Association

Abstract Valvular heart disease is common in systemic lupus erythematosus (SLE) and antiphospholipid syndrome. Immunologic insult plays a fundamental role in its pathogenesis but data on the role of antiphospholipid antibodies have been inconsistent, particularly regarding SLE-associated valvular lesions. Although timely diagnosis is essential to prevent progression of valvular lesions, treatment remains a challenge because of the lack of large systematic studies. This article reviews and summarizes recent information relating to valvular damage in these two autoimmune diseases, and highlights some important questions that need to be answered.

PALAVRAS-CHAVE
Lúpus eritematoso sistémico (LES);
Anticorpo antifosfolipídeo (AAF);
Doença valvular;
Tratamento;
Complicações;
Associação

As lesões valvulares nos doentes com lúpus eritematoso sistémico e síndrome antifosfolipídeo: uma velha doença, um desafio permanente

Resumo É elevada a prevalência da doença valvular no lupus eritematoso sistémico e na síndrome antifosfolipídeo. A lesão imunológica tem um papel primordial no desenvolvimento da doença valvular mas os estudos que suportam o papel dos anticorpos antifosfolipídeo na sua patogénese tem sido inconsistente. Apesar do diagnóstico atempado e precoce ser essencial na prevenção da progressão das lesões valvulares, a estratégia terapêutica continua a ser um desafio importante devido à falta de grandes estudos multicêntricos. Esta revisão pretende rever e sumariar toda a informação recente relacionada com a lesão valvular associada a estas doenças auto imunes bem como alertar os leitores para algumas questões que ainda não têm uma resposta imediata.

* Corresponding author.
E-mail address: luismoura@med.up.pt (L.M. Moura).

0870-2551/$ – see front matter
doi:10.1016/j.repc.2012.02.005

Introduction

The cardiovascular system is a frequent and characteristic target of several systemic autoimmune diseases, in particular systemic lupus erythematosus (SLE), a disorder that results in inflammatory damage in multiple organs. Libman–Sacks endocarditis was first described in 1924 by Emanuel Libman and Benjamin Sacks, who characterized this nonbacterial verrucous valvular disease in four patients with SLE.[1] Improvements in diagnostic techniques and better treatment with prolonged survival provide evidence that cardiac involvement can be potentially severe in SLE.[2,3]

The link between antiphospholipid antibodies (aPL) and Libman–Sacks endocarditis was first recognized in a case report published in 1985 by D'Alton et al., who reported a woman with SLE, positive lupus anticoagulant and verrucous endocarditis.[4]

Antiphospholipid syndrome (APS) or Hughes syndrome was first described in 1983 by Graham Hughes as anticardiolipin syndrome,[5] and is characterized by venous and/or arterial thrombosis, recurrent pregnancy loss and the presence of aPL. The term anticardiolipin syndrome was replaced by the term antiphospholipid syndrome when it became clear that antibodies against phospholipids other than cardiolipin were also associated with clinical manifestations of APS. This syndrome can be either primary or secondary to an underlying condition (most commonly SLE).[6–10]

Although typically mild and asymptomatic, Libman–Sacks endocarditis can lead to significant morbidity, being associated with serious complications such as superimposed bacterial endocarditis, thromboembolic events and severe valvular regurgitation and/or stenosis requiring surgery.[3]

Epidemiology

Cardiovascular complications have long been recognized as an important cause of morbidity and mortality in autoimmune disease. Valvular thickening is frequent in SLE patients, and valve vegetations in autopsy studies have been observed in 30–50%; however, symptomatic valvular disease with hemodynamic implications is rare.[3,10–12] To determine the real prevalence of Libman–Sacks endocarditis, several echocardiographic studies have been performed in recent years, some of which assessed the relationship between valvular lesions and aPL.

In the first prospective echocardiographic study, published in 1988, Galve et al. found clinically significant valvular lesions in 18% of patients with SLE (the prevalence of Libman–Sacks endocarditis was 9.5%).[13] Two years later Nihoyannopoulos et al. found an overall prevalence of cardiac involvement of 58%. The most common pathology was valvular (28%), ranging from thickened leaflets with impaired valve function (20%) to vegetations (9%), followed by pericardial involvement (21%) and myocardial dysfunction. The same report showed that high levels of anticardiolipin antibodies were strongly associated ($p < 0.0001$) with cardiac abnormalities, not only in SLE but also in other lupus-like syndromes.[14] Several other recent studies have analyzed the role of aPL. Some authors found an association between valvular abnormalities detected by transthoracic echocardiography and the presence of aPL.[14–18] However, other authors, who used transesophageal echocardiography, found no differences in the prevalence of valvular disease between patients with and without aPL.[19]

To clarify the relationship in patients with SLE between aPL and incidence and progression of severe valvular dysfunction requiring valve replacement, a Spanish research group recently published a prospective cohort study that enrolled 61 patients and 40 matched controls during 14 ± 3 years of follow-up. This long-term study found an increase of 39–73% in valvular abnormalities, but only 12% of patients developed severe valvular regurgitation. Until the publication of this study, attempts to identify patients at risk of developing severe valvular dysfunction had been unsuccessful. This group demonstrated that severe valvular regurgitation was significantly associated with the presence of high levels of IgG anticardiolipin antibodies ($p = 0.001$).[20] Another prospective cohort study that enrolled a significantly higher number of patients ($n = 342$) with a shorter follow-up period (four years) and with the same imaging modality (transthoracic echocardiography) determined the prevalence and progression of Libman–Sacks endocarditis. Of the 38 patients (11%) with Libman–Sacks endocarditis, nine progressed to more severe lesions during the follow-up period and eight new cases were diagnosed. This study reported a significant association between Libman–Sacks endocarditis and disease duration, activity, thrombosis, stroke, thrombocytopenia, anticardiolipin antibodies and APS.[21]

Pathogenesis of valvular lesions in SLE and APS

The pathogenesis of Libman–Sacks endocarditis is still unclear. The initial insult may be immunologic, as suggested by the presence of immunoglobulins and complement on affected valves. The deposition of fibrin-platelet thrombi onto the injured valve results in valve fibrosis, edema, diffuse thickening, mild inflammatory changes, valve distortion, scarring, and consequently valvular dysfunction.[22–24] Although there are no pathognomonic microscopic findings, it is common to see fibrin deposits, neovascularization, hyalinosis, calcinosis and a variable extent of inflammatory cell infiltration with mononuclear predominance. The end-stage of Libman–Sacks verrucous endocarditis can become a fibrous plaque sometimes showing focal calcification.[2,3,26] In this process the deposition of aPL under valves compromised by immune complex deposition can foster thrombus formation and inflammatory processes.[3,21–25] In a multicenter study Vianna et al. showed a significantly higher prevalence of valvular lesions in patients with APS secondary to SLE than in those with primary APS. This suggests that additional SLE factors involved in endocardial damage may play a specific pathogenetic role.[18] This process seems to be a continuous one that commences with immunologic lesions, evolves into valvular thickening and culminates with the formation of vegetations and their clinical consequences.

Diagnosis

Valvular lesions are frequent in patients with SLE and APS, but clinically significant valvulopathy occurs in only a small