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Evolution of cardiac dysfunction in patients with antiphospholipid antibodies and/or antiphospholipid syndrome: A 10-year follow-up study

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ABSTRACT

Objectives: To describe the evolution of valve involvement and myocardial dysfunction over time in patients with systemic lupus erythematosus (SLE) with or without antiphospholipid antibodies (aPL) and/or antiphospholipid syndrome (APS).
Methods: From an initial cohort of 150 patients assessed by transthoracic echocardiography 10 years ago, 17 patients with primary APS (PAPS), 23 with SLE-associated APS (SLE/APS), 19 with SLE positive for aPL without APS, and 23 with SLE negative for aPL were re-evaluated in the present echocardiography study.
Results: Valvulopathy was detected in 65% of PAPS and 62% of SLE patients with or without aPL. Disease duration [odds ratio (OR), 1.63; 95% confidence interval (CI), 1.13–2.36; $p = 0.009$ for every 5 years of increase] and presence of SLE/APS (OR, 3.51; 95% CI, 1.27–9.67; $p = 0.015$) were the only factors associated with the progression of valvular disease in univariate and multivariate analyses. Left ventricular diastolic dysfunction similarly progressed over time, with deceleration time (DT) and isovolumic relaxation time (IVRT) being equally prolonged in each of the four groups ($p < 0.05$). Right ventricular DT was significantly prolonged in each of the three SLE patient groups ($p < 0.001$), whereas IVRT increased only in SLE/APS patients ($p = 0.040$).
Conclusions: Among patients with APS and SLE (with or without aPL), SLE/APS and disease duration were independent factors for valvular disease progression in the present 10-year follow-up echocardiography study. Anticoagulation did not arrest valvular disease progression. Ventricular diastolic dysfunction, primarily of the left ventricle, also progressed over the 10-year period.

Introduction

Antiphospholipid Syndrome (APS) is an acquired, immune-mediated thrombophilia characterized by recurrent arterial and/or venous thromboses and/or pregnancy morbidity; it is defined by the presence of antiphospholipid antibodies (aPL), namely anticardiolipin antibodies (aCL), and/or anti-β2-glycoprotein I antibodies (anti-β2GPI), and/or lupus anticoagulant (LA) [1]. APS may occur alone (primary APS, PAPS) or in association with other autoimmune diseases, mainly systemic lupus erythematosus (SLE) (SLE/APS) [2].

In early reports, clinically important valve disease was recognized in nearly one-fifth of consecutive SLE patients [3], although frequencies as high as 74% were reported [4]. In subsequent studies in SLE patients, the presence of heart valve disease was associated with aPL [5,6]. This association was further supported by histological findings of fibrin strands and vasculopathy of the proliferating capillaries in valvular vegetations in patients with SLE and/or APS [7,8]. The subsequent reports were heterogeneous in terms of design, with some of them focusing clearly on the structural abnormalities of the valves either in SLE (with or without aPL) [9–11] or APS [12–14] and others emphasizing the functional disturbances of the myocardium in these patients [15–18].

Heart valvular involvement in patients with either SLE (with or without aPL) or APS (PAPS or SLE/APS) occurs and evolves with time in most follow-up studies [9,11,12,14,19]. Despite the echocardiographic progression of valvulopathy, its overall impact on cardiac function is small, with heart failure and need for valve replacement occurring infrequently (< 5%) [12]. A recent multicenter, retrospective study reported high mortality (12.5%) and morbidity rates (mainly thrombotic and bleeding events) in APS patients undergoing valve replacement surgery [20].

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Anticoagulation therapy or other immunotherapy usually does not halt progression of valvular disease [10,11,14]. However, improvement over time, especially of stenotic [10] or regurgitant [11] valves, has also been reported. Although discrepancy in these findings may reflect differences in methodology, it is likely that there is a knowledge gap in the evolution of the disease process. In most of these studies, the mean follow-up did not exceed 5 years and no other study, except one [19], compared PAPS with SLE/APS or SLE patients with or without aPL.

The present echocardiographic study included patients with PAPS and SLE/APS, SLE patients positive for aPL but without APS features, and SLE patients negative for aPL. The main objective of the study was to characterize the type and evolution of structural valvular abnormalities, as well as the myocardial dysfunction in these patients over a 10-year follow-up period. The above patient groups were selected in order to examine the independent role of either aPL or APS in the echocardiographic changes recorded over time.

Methods

Study cohort

All patients included in the present study were followed up at the Rheumatology Outpatient Clinic, Department of Pathophysiology, National University of Athens. They had been evaluated 10 years ago by transthoracic echocardiography and belonged to the following groups: (a) PAPS ($n = 26$), (b) SLE/APS ($n = 40$), (c) SLE positive for aPL without APS features (SLE/aPL/non-APS) ($n = 34$), and (d) SLE negative for aPL (SLE/non-aPL) ($n = 50$). The majority of this population ($n = 143$) constituted the initial cohort of a previous study on prevalence and characteristics of diastolic dysfunction published elsewhere [17]. The analysis of data regarding myocardial dysfunction included 128 patients after excluding cases with severe valvular disease, history of myocardial infarction, or alcohol abuse. Patients were evaluated every 6 months with physical and laboratory examinations. A second echocardiographic study was performed 10 years after initial echocardiographic evaluation.

Patients with APS met the Sydney classification criteria at the time of the second echocardiographic study [1]. Patients with SLE fulfilled at least four of the American College of Rheumatology SLE classification criteria [21].

The following clinical and laboratory parameters were recorded in all patients: ECLAM score for patients with SLE, biopsy-proven kidney involvement, serositis, livedo reticularis, venous and/or arterial thrombosis, pregnancy morbidity [22], systemic hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic pressure ≥ 90 mm Hg), hyperlipidemia (total cholesterol ≥ 200 mg/dL and/or triglycerides ≥ 150 mg/dL), the presence of diabetes mellitus, ANA, complement levels, anti-dsDNA, and antibodies to extractable nuclear antigens. Lupus anticoagulant (detected according to the guidelines of the International Society on Thrombosis and Haemostasis [23]) as well as IgG and IgM isotypes of aCL and anti-β2GPI antibodies (detected on two or more occasions 12 weeks apart) were also recorded and considered positive if their titers were >40 u or >99th percentile of the titers of 100 normal human sera, using solid-phase enzyme immunoassays (ELISAs) [1,24,25]. Medications including immunosuppressives, anticoagulant, and antiplatelet agents, as well antiarrhythmic and antihypertensive drugs, were recorded.

Echocardiography

Initial and follow-up echocardiographic measurements were carried out by the same operator (IM) blinded for disease status and study purpose, using a Hewlett Packard Sonos 1000 and 2500 ultrasound system with a 2.5 MHz transducer. Fractional shortening (FS) was used as a measure of left ventricular (LV) function and a FS $<29\%$ was considered compatible with LV systolic dysfunction. LV end-systolic and end-diastolic diameters, as well as interventricular septum and posterior wall thickness at end diastole, were measured to calculate FS [26]. RV systolic function was assessed from RV dP/dt derived from the tricuspid regurgitation velocity signal and from the tricuspid annular plane systolic excursion (TAPSE) [27–30].

Pulsed Doppler from mitral and tricuspid inflow velocity curves was used to calculate peak early velocity (E wave), peak velocity at time of atrial contraction (A wave), E/A ratio, deceleration time (DT) of the peak early velocity, and the LV isovolumic relaxation time (IVRT), with simultaneous recording of the LV inflow and outflow velocities. The RV-IVRT was defined as the time interval between closure of the pulmonary valve and opening of the tricuspid valve. This was estimated by subtracting the time interval between the peak of the R wave on the electrocardiogram and the end of the pulmonary systolic flow profile from the interval between the peak of the R wave and the onset of the tricuspid valve opening. For calculation of the RV systolic variables, at least three beats from end-inspiration and three beats from end-expiration were recorded and their values were averaged. Pulmonary artery systolic pressure (PASP) was estimated by continuous wave Doppler echocardiograms recorded in the apical four-chamber view as the peak systolic pressure gradient across the tricuspid valve (peak regurgitation velocity) plus the estimated right atrial pressure [31,32]. Intraobserver and interobserver variability of RV E wave, A wave, DT, and IVRT measurements in our laboratory were found to be as follows: 7.2% and 6.5% for E wave, 6.9% and 6.3% for the A wave, 5.9% and 5.6% for DT, and 5.4% and 5.1% for IVRT [17].

Valvular lesions were grouped into verrucous valvular vegetations (Libman–Sacks) [4,6] or diffuse valvular thickening and stiffness resulting in stenosis or regurgitation [9]. Doppler echocardiography was performed, beginning with color flow imaging. When abnormal intracardiac flow was detected, pulsed and continuous wave Doppler studies were performed. Mitral regurgitation was graded as mild, moderate, or severe, as previously stated [10].

Regurgitation seen only with Doppler and not associated with a murmur was considered normal. Combined valvular worsening was considered when a patient with the same affected valve in both echocardiograms had a deterioration of regurgitation or when a patient with stable valvulopathy of the same valve(s) in both echocardiograms or no valvulopathy at initial echocardiography presented with new-onset abnormal flows in another valve.

Statistical analysis

Patient characteristics were compared among different groups using parametric (*t*-test and ANOVA) and non-parametric (Mann–Whitney and Kruskal–Wallis) tests for continuous variables and χ^2 test or Fisher's exact test for categorical variables, as appropriate. The McNemar's and Stuart–Maxwell tests were used to compare valvulopathy and number of valves involved between initial and final patient evaluation. The effects of clinical and treatment parameters on the probability of valvulopathy worsening were evaluated with logistic regression models and expressed as odds ratios. Comparison of echocardiographic parameters between initial and final evaluations was performed using the Wilcoxon signed-rank test for paired samples. The association of changes with possible risk factors was examined univariately through Spearman correlation coefficients in the case of age and disease duration or using parametric (*t*-test and ANOVA) or non-parametric tests (Mann–Whitney and Kruskal–Wallis) in the case of categorical variables, such as the analysis group, arterial hypertension, and dyslipidemia, as appropriate. Results were considered statistically significant if $p < 0.05$.