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Original article

Arterial stiffness, antiphospholipid antibodies, and pulmonary arterial hypertension in systemic lupus erythematosus

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ABSTRACT

Background: The aim of this study is to evaluate the role of arterial stiffness in pulmonary arterial hypertension (PAH) in systemic lupus erythematosus (SLE) patients and its relationship with antiphospholipid antibody (aPL).
Methods: Measurement of brachial ankle pulse wave velocity (baPWV), carotid arterial stiffness, and pulmonary vascular resistance (PVR) was performed in 51 patients with SLE. PAH was diagnosed if the pulmonary artery systolic pressure was >40 mmHg. Information concerning SLE duration, medication, and serum autoantibodies was recorded. SLE activity was assessed by the SLE disease activity index (SLEDAI).
Results: aPL was present in 10 patients (20%), and PAH was detected in 6 patients (12%). The prevalence of Raynaud's phenomenon, baPWV, positive aPL, and titers of IgG anticardiolipin antibody (aCL) were increased in SLE with PAH; however, no difference was found in inflammatory markers, disease duration, and SLEDAI compared to SLE without PAH. Carotid artery deformation and right ventricular function were reduced in patients with PAH (all $p < 0.05$). Carotid artery circumferential strain ($r = 0.34$, $p = 0.021$), radial strain ($r = -0.30$, $p = 0.045$), and baPWV ($r = 0.46$, $p = 0.001$) showed significant correlation between IgG aCL. Univariate and multiple regression analysis revealed that the only significant independent predictors of the presence of PAH were baPWV, carotid artery stiffness, and IgG aCL.
Conclusion: Arterial stiffness might contribute to the pathogenesis of PAH related to SLE as well as aPLs. Furthermore, the significant association of aPL with arterial stiffness suggests its important role in PAH with SLE.

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Introduction

Pulmonary arterial hypertension (PAH) is a serious complication that is associated with a significant risk of death, and survival is significantly reduced in systemic lupus erythematosus (SLE) patients with PAH compared with those with idiopathic PAH (45% vs. 73% at 3 years) [1]. Estimates of the prevalence of PAH in SLE vary from 0.5 to 43% [2–5]. This wide variability in the reported prevalence rates reflects the differences in the definitions of PAH, diagnostic methods, population groups studied, and number of patients involved.

The etiology of PAH in SLE patients is not clear, but studies have shown an imbalance between vasoconstrictors and vasodilators in SLE-associated PAH, implying that endothelial dysfunction is a possible factor in its pathogenesis [6]. A role of inflammation in the development of PAH has also been suggested [7], and levels of inflammatory cells, including macrophages and lymphocytes, are increased in the plexiform lesions of hypertensive pulmonary vessels [8]. Although a causal relationship between SLE and PAH has not been established, the various elements of SLE, from vasculitis and in situ thrombosis to interstitial pulmonary fibrosis, can lead to endothelial and smooth muscle proliferation and damage of the pulmonary vasculature resulting in PAH.

In patients with SLE, antiphospholipid antibodies (aPL) are associated with arterial and venous thrombosis, and aPL accompanying SLE may form part of the pathophysiology of PAH [9,10]. They increased the risk of thrombosis and thromboembolism, and thrombogenic pulmonary vasculopathy has been documented in many patients with PAH [9,10]. Although some studies have suggested association of aPL with carotid artery intima-media thickness [11] and abnormal left ventricular diastolic filling [12], its association with arterial stiffness is uncertain. In this study,

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we evaluated the prevalence of PAH in a cohort of SLE and the role of arterial stiffness as well as disease-specific autoimmune or inflammatory markers in SLE–PAH. We hypothesized that if arterial stiffness plays a significant role in the pathogenesis in SLE–PAH, then the association with levels of aPL and arterial stiffness might be present.

Methods

Study population

Fifty-one SLE patients (aged 47.1 ± 14.7 years, 32 women) from the outpatient clinic of the rheumatology division who were diagnosed according to American College of Rheumatology criteria [13] were consecutively included. Exclusion criteria were smoking (in the last 5 years), diabetes mellitus, hypertension, hypercholesterolemia, renal failure, chronic hepatopathy, nephrotic syndrome, and hypothyroidism. Interstitial lung disease was excluded by high-resolution computed tomography, chronic thromboembolic pulmonary hypertension (CTEPH) was excluded by ventilation/perfusion lung scanning, and patients with evidence of congenital heart diseases, significant valvular disease, chronic obstructive pulmonary disease, portal hypertension, immunodeficiency virus, thyroid disorders, asplenia secondary to surgical splenectomy, sickle cell disease, thalassemia, chronic myeloproliferative disorders, and pregnancy were excluded. The study was approved by the Institutional Review Board and informed consent was obtained from all participants.

Echocardiographic examination

All echocardiography examinations were performed on a GE Vivid 7 ultrasound machine (GE Medical System, Horden, Norway) with a 2.5 MHz transducer. Two-dimensional and M-mode measurements were performed according to the recommendations of the American Society of Echocardiography. Left ventricular (LV) and right ventricular (RV) ejection fractions (EF) were estimated using modified Simpson's methods. Isovolumic contraction time (ICT), isovolumic relaxation time (IVRT), and ejection time derived from tissue Doppler imaging data were obtained, and the index of combined systolic and diastolic function [myocardial performance index; MPI = (ICT + IVRT) divided by ejection time] was calculated. The RV outflow tract (RVOT) time velocity integral (TVI_{RVOT}; in cm) was obtained by positioning the sample volume of the pulsed wave Doppler at the RVOT. Pulmonary vascular resistance (PVR) was calculated by the simple index of maximal tricuspid regurgitation velocity (TR Vmax)/TVI_{RVOT}, which is easy and quick to obtain and can provide important information about the degree of pulmonary vascular involvement. The Doppler-derived pulmonary artery systolic pressure (PASP; in mmHg) was then calculated from the TR Vmax using the simplified Bernoulli formula as follows: $PASP = 4 \times (TR\ Vmax)^2 + \text{right atrial pressure}$. PAH was defined as a PASP of at least 40 mmHg. RV function was measured using tricuspid annular plane systolic excursion (TAPSE), RV MPI, RV EF, and peak systolic strain at the base and mid-free wall side of RV assessed by tissue Doppler imaging. We also measured the global RV free wall strain by speckle tracking strain imaging. All echocardiographic examinations were performed by a single experienced operator (KI Cho) and then analyzed off-line with an EchoPAC Dimension system (General Electric) by the same operator blinded to the clinical status of study subjects.

Measurement of carotid arterial stiffness

We measured deformation parameters of the carotid arterial wall by speckle tracking strain imaging [14]. Circumferential peak systolic strain (%) was measured as an average of the whole circular region of interest (ROI) giving the respective 'global' strain. 'Global' values for radial strain could not be calculated due to limitations of the EchoPAC software and consequently radial peak systolic strain was only obtained 'regionally' from a discrete point (20 × 20 pixels) located in the far wall of the vessel. During systole, circumferential strain assumes positive values due to stretching or expansion of the vessel wall whereas radial strain becomes negative as a result of compression of the vessel wall. The frame rate for the two-dimensional strain was 60 ± 15 frames/s, and the ROI was placed at the adjacent arterial wall if plaque existed. Interobserver and intraobserver variations for strain were 10% and 12%, respectively.

Measurement of peripheral arterial stiffness

Arterial stiffness was assessed by measuring brachial-ankle pulse wave velocity (baPWV) using an automatic waveform analyzer (VP-1000; Colin Co., Komaki, Japan) [15]. The VP-1000 simultaneously records pulse waves, blood pressure (both arms and ankles), ankle-brachial pressure index (ABI), electrocardiogram, and heart sounds, as described elsewhere [16]. For measuring baPWV, pulse waves obtained from the brachial and tibial arteries were recorded simultaneously, and the transmission time, defined as the time interval between the initial increase in brachial and tibial waveforms, was determined. The transmission distance from the arm to each ankle was calculated according to the body height. The baPWV was automatically computed as the transmission distance divided by the transmission time. All participants included in the present study had a normal ABI (>0.9).

Disease-specific evaluation

Disease activity was assessed by the SLE disease activity index (SLEDAI) [17]. All SLE patients and controls fasted for at least 12 h at the beginning of the study before blood tests. Peripheral blood cell counts were determined using an automated hematology analyzer (SE-9000; Sysmax, Kobe, Japan). In terms of immunological parameters, we measured anti-double stranded DNA antibodies (anti-dsDNA Ab) by enzyme immunoassay (EIA) with the Bio-Flex DNA ds test (Bioflex, Japan), which does not react with single-stranded DNA (reference: IgG ≤ 4 IU/ml, IgM ≤ 20 IU/ml), and antinuclear antibody (ANA) and complement concentrations on an autoanalyzer (ADIVA 1800; Siemens, New York) by turbid immunometry (reference: C3 50–90 mg/dl, C4 10–40 mg/dl). The β2 glycoprotein I (GPI)-dependent anti-cardiolipin antibody (aCL) titers were determined using EIA (DRVVT; Diluted-Russell, S-Viper-Venom Test) and defined positive as IgG or IgM anticardiolipin >12 IU/ml or the presence of lupus anticoagulant. The anti-Ro antibody (reference: ≤1.0 AI), anti-La antibody (reference: ≤1.0 AI), anti-Smith (Sm) antibody (reference: ≤1.0 AI), and antiRNP antibody (reference: ≤1.0 AI) were also measured by EIA. The plasma concentrations of high sensitivity C-reactive protein (hsCRP) were measured using fully automated turbid immunometry (Advia 1800). ANA levels were also determined in controls to exclude the presence of autoimmune diseases.

Statistical analysis

Statistical analysis was performed with the statistical program SPSS for Windows version 12.0 (Chicago, IL, USA). Results are presented as mean ± standard deviation (SD) or percentage. Comparisons were performed between patients and control groups using Student's *t*-test for quantitative variables and chi-square or the exact Fisher test for qualitative variables. Comparison between patients with and without PAH was performed by Mann–Whitney *U* test. Correlations between variables were assessed by calculating

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