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Review

Pulmonary hypertension in systemic lupus erythematosus: prevalence, predictors and diagnostic strategy

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ABSTRACT

Objectives: To investigate the prevalence and predictors of pulmonary hypertension (PH) in patients with systemic lupus erythematosus (SLE) and to validate a diagnostic strategy.
Methods: 245 patients with SLE entered a screening program. Possible PH was defined as two consecutive systolic pulmonary arterial pressure (PAP) values ≥ 40 mm Hg by echocardiography. The subsequent diagnostic procedure, including right heart catheterization if needed, confirmed or excluded the diagnosis of PH secondary to cardiopulmonary disease or SLE-related pulmonary arterial hypertension (PAH). Independent predictors of PH were identified by multivariant multiple linear or logistic regression models. The sensitivity (S), specificity (SP), positive (PPV) and negative predictive values (NPV) were calculated for different screening cutoff values.
Results: 88% patients were women. The mean (SD) age at the time of enrolment was 45 (16) years. 12 cases of PH were detected, all secondary, with a resulting prevalence of 5%. Two consecutive echocardiographic PAP measurements ≥ 40 mm Hg performed best as the cutoff point for screening (S 100%, SP 97%, PPV 70, NPV 100), as compared with single PAP measurements ≥ 30 mm Hg or ≥ 40 mm Hg The age at the time of enrolment was the only variable independently associated with PAP values ($p = 0.0001$), with the SLICC damage index score showing a borderline association ($p = 0.08$). Only the age at the time of enrolment showed an independent association with PH (OR 1.10, 95% CI 1.06–1.17).
Conclusion: We found a low prevalence of PH. Screening echocardiograms in asymptomatic lupus patients are thus not recommended. Two consecutive PAP values ≥ 40 mm Hg by echocardiogram is the best screening cutoff for starting investigations in SLE patients with suspected PH.

Contents

Abbreviations: SLE, systemic lupus erythematosus; PAP, pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; TJV, tricuspid jet velocity; RVSP, right ventricular systolic pressure; PAD, right atrial pressure; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; SD, standard deviation; S, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; SDI, systemic lupus international collaborating clinics damage index; SLEDA, systemic lupus erythematosus disease activity index.

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1. Introduction

Pulmonary hypertension (PH) is characterized by the progressive increase in pulmonary vascular resistance, eventually leading to right ventricular failure. It is defined as a resting mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg measured by right heart catheterization. For the diagnosis of the subclass known as pulmonary arterial hypertension (PAH), a measured pulmonary arterial wedge pressure < 15 mm Hg is required [1,2]. Transthoracic Doppler echocardiography is the most widely used screening test for PH in the presence of clinical suspicion and/or predisposing conditions [2], despite the fact that echocardiography can miss asymptomatic patients with early mild PH [3]. Right heart catheterization is considered the definitive diagnostic method [2,3].

The clinical classification of PH was last updated in 2008 [3], with PAH associated with systemic autoimmune diseases being included within the Group I. Indeed, PAH is a recognized complication of systemic sclerosis, and, much less frequently, systemic lupus erythematosus (SLE) [4,5]. In addition, PH in SLE can be secondary to chronic thromboembolic disease or cardiopulmonary complications [3,5].

PH has been identified as a predictor of morbidity and mortality in SLE [6,7]. Several variables have been proposed as potential risk factors for PH: Raynaud's phenomenon [6,8–10], antiphospholipid antibodies [11,12], antiU1-RNP antibodies [8,13] and disease activity [8,14]. The prevalence of PH is variable across the different lupus cohorts, ranging from less than 2% [15] to 43% [16]. Such discordant results may actually reflect the varying definitions of PH and the differences in the diagnostic protocols. In fact, there are no standardized guidelines for the screening of PH in SLE.

2. Methods

2.1. Study design and objectives

This cross-sectional study has the main objective of establishing the prevalence of PH and PAH in an observational longitudinal cohort of SLE patients. The secondary objectives were to identify potential predictors for PH and to validate a screening program to detect PH in lupus patients.

2.2. Patients

The Lupus-Cruces cohort is a longitudinal observational cohort joining SLE patients fulfilling the 1997 classification criteria of the American College of Rheumatology [17]. At enrolment, all patients signed an informed consent authorizing the use of their clinical data for epidemiological studies. The local institutional review board approved the Lupus-Cruces cohort study and the informed consent form.

At each follow-up visit, different variables are collected in a database: demographic characteristics (age, sex, race, year of diagnosis, death and cause of death) manifestations of SLE (clinical, target organ involvement), autoantibody profile (anti DNA, anti-Ro, anti-La, anti-RNP, anti-Sm, antiphospholipid), treatment received (glucocorticoids, immunosuppressives, antimalarials, anticoagulants…) and complications of the disease and/or treatment (infections, renal transplantation, osteoporosis, diabetes, retinopathy, cancer). The systemic lupus international collaborating clinics (SLICC) damage index (SDI) [18] is calculated yearly. The systemic lupus erythematosus disease activity index (SLEDAI) [19] was calculated in retrospect.

A screening program for detecting PH was carried out between October 2004 and December 2009. The 245 lupus patients on active follow up entered the screening program, irrespective of the presence of dyspnea.

2.3. Pulmonary hypertension screening

A Philips SONOS 7500 echocardiography, 3-MHz probe, including two-dimensional anatomical image, M mode echocardiography and Doppler was used for this study. All the studies were performed by the same two cardiologists specialized in echocardiography. An estimation of the pulmonary artery systolic pressure (PAP), equivalent to the right ventricular systolic pressure (RVSP) in the absence of obstruction of pulmonary outflow tract, was calculated using the modified Bernoulli equation: RVSP = 4v2 + PAD, where v is the measured tricuspid jet velocity (TJV), and PAD is the estimated right atrial pressure, predetermined at 5 mm Hg. According to recent international guidelines, an estimated PAP value ≥ 40 mm Hg was considered the suggestive limit for PH [2].

At least one transthoracic echocardiography was performed to each patient. According to the study protocol, all patients with a PAP ≥ 40 mm Hg had a second echocardiogram done within a period of 6 months to 1 year. Additional echocardiograms were performed in the remaining patients at the discretion of the attending physician.

Patients with two serial estimated PAP ≥ 40 mm Hg were considered candidates for further study. The subsequent diagnostic process included, depending on the clinical situation and TJV measured in the echocardiograms, additional echocardiograms and clinical observation, pulmonary function tests, chest computed tomography, ventilation/perfusion lung scan, 6-minutes walking test and, eventually, a right heart catheterization in order to establish the definitive diagnosis of secondary PH or SLE-related PAH.

2.4. Working definitions

Possible PH was defined as two consecutive echocardiograms with PAP ≥ 40 mm Hg.

Secondary PH was diagnosed in patients with possible PH plus one of the following conditions: cardiomyopathy with systolic or diastolic dysfunction, moderate-severe valvular dysfunction, restrictive lung disease, chronic pulmonary thromboembolism or severe chronic obstructive pulmonary disease [3]. Patients with a right heart catheterization showing a resting mPAP ≥ 25 mm Hg and a measured pulmonary arterial wedge pressure ≥ 15 mm Hg were also diagnosed of secondary PH [2,3].

SLE-induced PAH was diagnosed in the presence of a resting mPAP ≥ 25 mm Hg plus pulmonary arterial wedge pressure < 15 mm Hg measured by right heart catheterization [2,3].

2.5. Statistical analysis

The clinical descriptors of our cohort were generated, using means with standard deviation (SD) or proportions, as indicated. The prevalence of possible PH and definite PH, both secondary and SLE-associated PAH, was calculated. In order to identify the possible predictors of PAP values, PH and PAH, the following strategy was followed: univariate linear regression was performed on each possible predictor of the first PAP value. Likewise, univariate conditional logistic regression was performed on each of the same independent variables to test their association with PH. The same analysis would be performed with PAH as the dependent