Prevalence and risk factors for pulmonary arterial hypertension in patients with lupus

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Objectives. Pulmonary arterial hypertension (PAH) is associated with rapid deterioration and poor prognosis in SLE, especially during pregnancy. The prevalence of PAH in SLE in non-tertiary centres is uncertain. This study aims to estimate the point prevalence of PAH and identify risk factors for PAH in a large cohort of SLE patients.

Methods. A prospective cross-sectional study of 288 patients with SLE were recruited from lupus clinics in Birmingham, UK. Resting transthoracic echocardiography was performed to estimate the pulmonary artery pressures and to assess cardiac morphology and function. PAH was defined as systolic pulmonary artery pressure (sPAP) >30 mmHg. We assessed potential risk factors such as the presence of lung disease, respiratory muscle weakness, autoantibodies, smoking, RP and APS.

Results. Of 288 patients who consented for participation, 283 patients were suitable for analysis. Twelve patients were found to have PAH with sPAP >30 mmHg. The range of sPAP in our PAH patients was 31–59 mmHg and three patients had sPAP >40 mmHg. The only significant risk factor for PAH was LAC (P = 0.005).

Conclusions. The point prevalence of PAH was 4.2% in our cohort of patients with SLE. Most of the PAH cases were found to be of mild severity (<40 mmHg). The significant association of LAC and presence of APS in PAH cases suggests that thrombosis may play an important role in PAH with SLE. This is important, as it is treatable.

Key words: Systemic lupus erythematosus, Pulmonary arterial hypertension, Prevalence, Echocardiography, Lupus anti coagulant, Screening, Risk factors, Anti-phospholipid antibodies.

Introduction

SLE is a well recognized autoimmune multisystem disorder with frequent respiratory and cardiac manifestations that can lead to significant morbidity and mortality. Pulmonary hypertension is a serious complication that is associated with a significant risk of death especially in pregnancy in the early post-partum period [1–3]. In the last few years, new treatment modalities have been developed to improve the symptoms and prognosis of pulmonary hypertension [4, 5]. Most of these studies have been performed in idiopathic pulmonary arterial hypertension (PAH) patients and in connective tissue disease patients with SSC.

Estimates of the prevalence of PAH in SLE vary from 0.5 to 43% [6–9]. These results are from retrospective studies of large groups of patients over a period of 5–10 years or cross-sectional studies involving small numbers of SLE patients. The wide variability in the reported prevalence rates reflects the varying definitions of PAH used, differences in diagnostic methods, population groups studied and number of patients involved. There have been no attempts at diagnosing PAH in large cohorts of SLE.

The non-specific nature of symptoms such as dyspnoea, palpitations, fatigue and syncope associated with PAH could lead to a delay in the diagnosis of PAH in patients with SLE. This suggests a need for appropriate screening methods to identify PAH. Although the gold standard test to diagnose PAH is right heart catheterization (RHC), this is an invasive and expensive test, which makes it unsuitable for use as a screening tool. Transthoracic Doppler Echocardiography has, however, been shown to be a safe, sensitive and specific tool to screen for PAH as well as to assess the severity of PAH in patients with SSc [10, 11]. Using this technique, we set out to prospectively determine the prevalence of PAH in our SLE cohort and to assess risk factors that may play a role in the development of PAH in SLE patients. We also assessed the value of pulmonary function tests and dyspnoea screening questionnaires as screening tests for PAH.

Methods

Detailed methods are available as supplementary data at Rheumatology Online.

Patient recruitment

This prospective cross-sectional study was conducted in the Wellcome Trust Clinical Research Facility (WTCRF) at the Queen Elizabeth Hospital (QEH), Birmingham, UK, between January 2004 and December 2005. This study was carried out in accordance with Helsinki declaration and received ethical approval from multicentre research ethics committee, UK (MREC 03/9/067). Three hundred and ninety-two patients with SLE were invited to take part in this study. Two hundred and eighty-eight (73%) patients gave informed written consent to participate. Two hundred and eighty-five (99%) patients fulfilled four criteria for SLE diagnosis defined by 1982 revised ACR criteria [12], whereas the remaining patients fulfilled three criteria and a clinical diagnosis of SLE by the Consultant Rheumatologist responsible for patient’s care (C.G. or R.D.S.).

At the initial visit, a detailed clinical evaluation including history of smoking and RP plus, ECG, assessment of SLE disease activity using BILAG index [13, 14] and the SLICC/ACR damage index [15, 16] scores was undertaken. Echocardiography (ECHO) and the screening tests and assessments of risk factors for
PAH were performed either at the same visit or within 4 weeks of this assessment.

**ECHOCARDIOGRAPHY**

CHO. All patients had echocardiographic examinations performed at rest using a Sonos 7500 echocardiogram (Philips Medical systems) by an experienced echocardiographer. Scan results were reviewed by consultant cardiologists. Grade A refers to the most active score in each organ or system necessitating prescription of high-dose steroids or immunosuppressive therapy. Grade B refers to a previously involved system but no current activity and Grade C refers to patients with disease activity requiring lower dose steroids, anti-malarials or NSAIDs. Grade D refers to systems that have never been involved. The SLICC/ACR damage index [15, 16] describes the accumulated damage in 12 organ/systems since the diagnosis of SLE.

**Confirmation of PAH by RHC**

All patients who were found to have severe PAH with sPAP >40 mmHg with New York Heart Association (NYHA) class 3 or 4 dyspnoea were offered referral to a cardiologist for consideration of RHC. Patients with PAH that did not meet these criteria were not offered this invasive test at the request of the ethics committee as they felt that the risks outweighed the benefits [21].

**Assessment of risk factors for PAH**

**Autoantibodies.** The autoantibodies were measured using kits from The Binding Site, UK.

**Respiratory muscle strength.** The inspiratory and expiratory muscle strength measurements were performed using handheld respiratory pressure meter (MicroRPM, Micro Medical Ltd).

**Pre-existing lung disease.** The presence of SLE-related lung diseases in these patients were obtained from clinical examination, pulmonary function tests, chest X-ray and high-resolution CT chest.

**BILAG index and SLICC/ACR damage index.** The BILAG index [13, 14] is a valid, reliable and comprehensive clinical measure of lupus disease activity. This index reports disease activity in eight organ/systems separately and is based on the scores calculated for each system depending on the presence of clinical features. The scores were determined using the BLIPS (British Lupus Integrated Prospective System) software programme. The scores are graded A through to E. Grade A refers to the most active score in each organ or system necessitating prescription of high-dose steroids or immunosuppressive therapy. Grade B applies to those patients with disease activity requiring lower dose steroids, anti-malarials or NSAIDs. Grade C refers to patients with mild features only needing symptomatic therapy. Grade D refers to a previously involved system but no current activity and Grade E applies to systems that have never been involved. The SLICC/ACR damage index [15, 16] describes the accumulated damage in 12 organ/systems since the diagnosis of SLE.

**Screening tests for PAH**

(i) 6MWT was performed according to international guidelines [22].

(ii) The respiratory symptom questionnaires used in this study were St George's respiratory symptom questionnaire (SGRQ) [23, 24], modified Medical Research Council (MRC) [25] dyspnoea scale and baseline dyspnoea index (BDI) [26, 27].

(iii) *Pulmonary function testing.* Forced vital capacity (FVC) was measured using the Jaeger Compact system (Viasys Healthcare). Total lung capacity (TLC) and residual volume (RV) were measured by single-breath technique (Jaeger Compact system). Results were expressed as the percent of predicted values.

**Statistical analysis**

Data were analysed with the SPSS 13.0 statistics package. Variables are summarized as counts and/or percentages or as medians and ranges. Comparisons between groups were made using the two-tailed Fisher's exact test or Mann-Whitney U-test. Association between variables were assessed with Spearman rank correlation. The P-values quoted have not been adjusted for multiple comparisons as this is an exploratory study aiming to identify possible risk factors. A Bonferroni correction would not be appropriate as the risk factors are not independent of each other.

**Results**

**Demographics**

Two hundred and eighty-three patients with SLE were studied and 266 patients (94%) were females. The median age was 41 years (range 18–82 years) and median disease duration was 8.7 years (range 0–32 years). RP occurred in 66.4%, and 63.6% were non-smokers. APS [28] was known to be present in 12.4%. The racial distributions for Afrocaribbean, Indian Subcontinent, Caucasian, Oriental and others were 18.7, 19.8, 56.2, 0.7 and 4.6%, respectively.

SLICC/ACR damage index scores revealed that 57.2% did not have any organ damage. A total of 9.9% had cardiac or pulmonary damage secondary to SLE. At the time of this study, only 29.3% had active SLE in one or more of the eight organ/systems scoring A or B using assessment by BILAG index [14]. Two-thirds of these patients had evidence of activity either in the musculoskeletal or haematological system.

**Prevalence of PAH**

Among the 288 patients with SLE that took part in the study, 5 patients were excluded from analysis as their echocardiographic views were very limited and thus the echocardiographer was unable to estimate the PAP. Of the remaining 283 patients, TR was absent in 114 (40.3%) patients by ECHO assessment. In all of these cases, there were no other echocardiographic features (right ventricular dilatation or hypertrophy) to suggest PAH. Among the 169 patients in whom TR was present, 12 were estimated to have sPAP >30 mmHg at rest. According to the definition of PAH used in this study, the point prevalence rate of PAH in patients with SLE was 4.2% (95% CI 2.2, 7.3). Excluding patients with no TR, the prevalence of PAH in our study group would be 7.1% (95% CI 3.7, 12.1).

The distribution of PAP among the 169 patients in the latter group is shown in Fig. 1. Only one patient was previously known to have PAH diagnosed by ECHO. There were four other patients with a previous history of PAH who did not meet the criteria for PAH in this study. The characteristics of these patients...
with previous PAH diagnosed by ECHO are shown in Table 1. Among the remaining 109 patients in our cohort (104 who refused to participate in this study and 5 whose echo assessment was not suitable for analysis), 3 patients (2.7%) had had PAH diagnosed by ECHO in the past.

**Risk factors**

**Autoantibodies.** The presence of ANA, dsDNA, ENA, low complements C3/C4, aCL and LAC were compared between PAH cases and non-PAH patients. LAC ($P = 0.005$) was significantly associated with PAH, whereas other antibodies did not show any difference between both groups (Table 2). Some results were not available for ENA (6/283) and LAC analysis (67/283) due to either technical reasons (no result from the laboratory) or patients being on warfarin therapy and not suitable for testing of LAC (Table 2).

**Respiratory muscle strength.** Six out of 11 PAH cases had inspiratory and/or expiratory muscle weakness but there was no association between respiratory muscle strength and PAH in this study (Table 3). Eighteen patients were unable to or refused to perform this test.

**Presence of underlying lung disease.** The restrictive lung conditions found in 14 patients in this cohort included pulmonary fibrosis, shrinking lung syndrome, pleural thickening, and the obstructive lung diseases in 27 patients included asthma and...
Table 4. Frequency of prior drug therapy among SLE patients with and without PAH

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>Prior use in SLE patients without PAH (n=271)</th>
<th>Prior use in SLE patients with PAH (n=12)</th>
<th>P-value (Fisher’s exact test, two sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>26 (9.6)</td>
<td>5 (41.7)</td>
<td>0.005**</td>
</tr>
<tr>
<td>Aspirin</td>
<td>107 (39.5)</td>
<td>4 (33.3)</td>
<td>0.770</td>
</tr>
<tr>
<td>CCB</td>
<td>58 (22.9)</td>
<td>6 (50)</td>
<td>0.031*</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>61 (22.5)</td>
<td>1 (8.3)</td>
<td>0.474</td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.01. CCB: Calcium channel blockers; ACE inhibitors: angiotensin converting enzyme inhibitors.

chronic obstructive airways disease (COPD). Only two patients with PAH had previous lung disease. One patient had shrinking lung syndrome and the other had asthma. There was no significant difference between SLE patients with and without PAH in relation to the presence of restrictive and/or obstructive lung diseases (Table 3).

Smoking, RP and APS. The association of clinical APS with PAH in SLE was considered borderline (Table 3; P = 0.043), whereas RP and smoking were not statistically significant.

Prior drug therapy. The distribution of drug therapy in the study cohort is shown in Table 4. The prior use of warfarin (P = 0.005) and calcium channel blockers (P = 0.031) were found more frequently with PAH in SLE. None of the patients was on Sildenafil or Bosentan prior to this study.

Screening tests

Six-min walk test. Two hundred and seventy-seven patients performed this test and the median distance walked in 6 min (6MWD) in PAH group was 435 m (range 150–600 m) and in non-PAH group was 440.5 m (range 60–729 m). Six patients were unable to perform this test due to walking difficulties, fatigue or refusal to perform it. There were no significant correlation between the 6MWD and sPAP in either group. The fatigue and dyspnoea scores pre- and post-exercise were not significantly different between patients in the PAH group and non-PAH group.

Respiratory symptom questionnaires. SGRQ: The median total score in the PAH group was 23.9 (range 3–77.8) and in the non-PAH group was 18.9 (0–82.2) (P = 0.506), respectively. Similarly, the modified MRC dyspnoea scale and the BDI were not statistically significant in differentiating patients with and without PAH (data not shown).

Pulmonary function tests. None of the parameters tested was significantly different between patients with and without PAH. The median predicted values of TLCO were <80% in both groups: median (and range): 66% (36–100%) in the PAH group and 75% (16–127%) in the non-PAH group.

Cardiac catheterization. Only one of three patients with sPAP >40 mmHg had NYHA grade 3 dyspnoea and was eligible for cardiac catheterization. This patient refused to undergo this invasive test.

Discussion

In this study, we found that the prevalence rate of PAH in patients with SLE was 4.2%. If patients with no TR jet on ECHO were excluded from the analysis, the prevalence rate was 7.1%. These rates are at the lower end of the range of prevalence rates reported from previous studies [6, 7, 9, 29]. This prospective cross-sectional cohort study is likely to reflect the prevalence rate better than the previous retrospective and smaller studies. The majority (80.4%) of this cohort have Birmingham postcodes, suggesting that the majority are from local community rather than a patient cohort mainly referred from other centres for tertiary care. The SLICC/ACR damage index scores recorded as part of this study were low, suggesting that only few patients had severe disease. It has been suggested that studies with predominantly a tertiary care-based cohort [6] and/or patients with severe SLE [7] are likely to underestimate the true prevalence of PAH. We believe that our cohort has minimal bias from these factors resulting in a more accurate estimation and lower prevalence rate of PAH in SLE patients. Those patients who refused to participate (n = 104; 27%) could have done so for various reasons including active disease, lack of interest in participating in research studies, inconvenience due to distance required to travel to the centre and work commitments. We are not aware of any main reason for non-participation.

In this study, TR velocity was measurable in 169 patients (59.7%). This is in keeping with previously reported frequencies of identifying measurable TR in the range of 39–86% of patients [30, 31]. This frequency increases to almost 100% in patients with signs of right heart failure and those with sPAP >50 mmHg [32]. The inter-observer variability in the measurement of maximal TR velocity has been found to be <3% [33]. Several studies have shown significant correlation between RVSP measured by Doppler ECHO and mean PAP measured by RHC [11, 20, 31, 34].

Of 12 patients with PAH, 9 had sPAP <40 mmHg and 10 had NYHA Grade 2 dyspnoea or less. This suggests PAH in this SLE cohort was predominantly mild with minimal or no symptoms. In the PAH group, only one patient each had restrictive lung disease, known valvular heart disease and previously recorded PAH. This supports the mild nature of cardio-respiratory manifestations and lack of significant dyspnoea in our PAH cases. The role of left heart disease is negligible in our patients with PAH as none of them had significant left ventricular dysfunction with or without valve disease evaluated by ECHO.

Most of our patients with systemic hypertension or RP were on treatment with vasodilators such as calcium channel blockers (CCB) and angiotensin converting enzyme (ACE) inhibitors. Thirty-one out of 283 patients with previous thromboembolic disease and/or APS were on anti-coagulant therapy. The significant association of prior use of warfarin and CCB (Table 4) suggests the possible role of these drugs in either lowering the sPAP or preventing the sPAP from rising to significantly higher values indicative of PAH, as well as supporting the hypothesis that there may be a thrombotic mechanism underlying the pathogenesis of PAH in these SLE patients.

The pulmonary function test parameters had no value as a screening test for PAH in our cohort with mild PAH. This is in keeping with results from previous studies [35] involving mild cases of PAH. Similarly, 6MWT and respiratory symptom questionnaires failed to show any significance as a screening test for PAH in this cohort. In contrast to previous studies, RP [36] and presence of lung disease do not increase the risk of PAH in this SLE cohort.

In this study, LAC was the only significant risk factor for PAH in SLE [37]. This, in addition to the borderline significance of clinical APS, suggests the role of thrombosis as a mechanism in the pathogenesis of PAH in our SLE patients. However, a recent study by Farzaneh-Far et al. [38] on 200 patients from a tertiary care lupus cohort with a PAH prevalence of 17.5% did not find any association with anti-phospholipid antibodies, defined as IgG or IgM aCL titre >40 IU/ml [39] and/or positive LAC. When we increased the sPAP threshold to >35 mmHg for PAH we found a statistically significant association between aPLs (aCL and/or LAC) and PAH (P = 0.005; data not shown) though numbers were small.
We would suggest that screening for PAH in SLE patients should be recommended only in symptomatic patients and/or high-risk groups such as those planning pregnancy. It has been well documented that PAH in pregnancy carries a poor prognosis [1]. A review of published reports by Weiss et al. [2, 3] revealed maternal mortality of 56% with secondary PAH compared with 30% with primary PAH. All maternal deaths occurred within 5 weeks post-partum and the most critical period is the first 72 h after delivery [40]. In the first 72 h post-partum, the cardiac output increases secondary to maternal auto transfusion and increased venous return to right heart. In PAH, there is increased pulmonary vascular resistance such that this high cardiac output status results in right heart failure that can cause death. We have previously reported such a death from PAH in an SLE patient [40]. The maternal prognosis depends on early diagnosis, early hospital admission and individually tailored treatment during pregnancy with particular attention to medical care post-partum. Rapid deterioration of PAH occurs when pulmonary thromboembolic disease complicates PAH [40]. The risk is highest in those with a prothrombotic tendency such as APS during pregnancy.

This study has limitations. First, about a quarter of eligible patients (27%) refused to take part. It is possible that the assessment of our screening tools may have been biased by this non-participation. However, we could not identify any single reason for non-participation. Secondly, our measurements of PAP were indirect and not backed up by the gold standard RHC. Despite this, we have used echocardiographic screening criteria used by several other studies and our ethics committee felt it unethical to catheterize patients with only mild/asymptomatic disease.

**Conclusion**

The majority (75%) of our PAH cases were mild and asymptomatic and as such would not meet the criteria for guideline-based treatment [41]. Furthermore, it is currently unclear whether establishing the diagnosis of PAH in the pre-symptomatic phase improves outcome. In the light of these results, we recommend screening by ECHO for this complication only in high-risk groups such as those planning pregnancy, especially those with positive LAC with or without a clinical history of APS [1–3, 40].

**Rheumatology key messages**

- The prevalence of PAH was 4.2% in a community-based lupus cohort and the majority were mild.
- LAC was the only significant risk factor for this complication of lupus.

**Acknowledgements**

D.T. is funded by the Wellcome trust.

**Funding: This study was supported by an unrestricted educational grant from Actelion Pharmaceuticals Limited, UK.**

**Disclosure statement: C.G. has received an unrestricted educational grant that funded this work and honoraria for lectures and attendance at a scientific advisory board from Actelion Pharmaceuticals. C.-S.Y. is funded by an unrestricted educational grant from Asperva Pharmaceuticals and is a consultant to Roche. They have also received honoraria from Roche and Merck Serono for providing training sessions on Classic BILAG and BILAG-2004 indices. A.P. has received an educational grant for his clinical research fellowship from Actelion Pharmaceuticals. All other authors have declared no conflicts of interest.**

**Supplementary data**

Supplementary data are available at Rheumatology Online.

**References**


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