Systemic lupus erythematosus and pulmonary arterial hypertension: links, risks, and management strategies

Konstantinos Tselios
Dafna D Gladman
Murray B Urowitz

University of Toronto Lupus Clinic,
Centre for Prognosis Studies in the Rheumatic Diseases, University Health Network, Toronto, ON, Canada

Abstract: Systemic lupus erythematosus (SLE) is characterized by the second highest prevalence of pulmonary arterial hypertension (PAH), after systemic sclerosis, among the connective tissue diseases. SLE-associated PAH is hemodynamically defined by increased mean pulmonary artery pressure at rest (≥25 mmHg) with normal pulmonary capillary wedge pressure (≤15 mmHg) and increased pulmonary vascular resistance. Estimated prevalence ranges from 0.5% to 17.5% depending on the diagnostic method used and the threshold of right ventricular systolic pressure in studies using transthoracic echocardiogram. Its pathogenesis is multifactorial with vasoconstriction, due to imbalance of vasoactive mediators, leading to hypoxia and impaired vascular remodeling, collagen deposition, and thrombosis of the pulmonary circulation. Multiple predictive factors have been recognized, such as Raynaud’s phenomenon, pleuritis, pericarditis, anti-ribonuclear protein, and antiphospholipid antibodies. Secure diagnosis is based on right heart catheterization, although transthoracic echocardiogram has been shown to be reliable for patient screening and follow-up. Data on treatment mostly come from uncontrolled observational studies and consist of immunosuppressive drugs, mainly corticosteroids and cyclophosphamide, as well as PAH-targeted approaches with endothelin receptor antagonists (bosentan), phosphodiesterase type 5 inhibitors (sildenafil), and vasodilators (epoprostenol). Prognosis is significantly affected, with 1- and 5-year survival estimated at 88% and 68%, respectively.

Keywords: systemic lupus erythematosus, pulmonary arterial hypertension, immunosuppressive, transthoracic echocardiogram, endothelin receptor antagonists

Introduction

Pulmonary arterial hypertension (PAH) is classified into five distinct categories according to etiology. Group 1 PAH may be idiopathic, heritable, or drug or toxin induced, or it could be associated with human immunodeficiency virus, schistosomiasis, portal hypertension, and congenital heart disease as well as with connective tissue diseases (CTDs). PAH related to left heart diseases is classified in group 2, lung diseases in group 3, chronic thromboembolic pulmonary hypertension in group 4, while other, less well-known causes are included in group 5. CTD-associated PAH is hemodynamically defined by increased mean pulmonary artery pressure at rest (mPAP ≥25 mmHg), with normal pulmonary capillary wedge pressure (PCWP ≤15 mmHg) and increased pulmonary vascular resistance (PVR). Systemic lupus erythematosus (SLE) is characterized by the second highest prevalence of PAH, after systemic sclerosis, according to the REVEAL registry (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension disease management), a 55-center longitudinal US-based registry with nearly 3,500 patients. The aim of this review is to present the current knowledge on
the epidemiology, pathophysiology, diagnosis and treatment of SLE-associated PAH (SLE-PAH).

**Epidemiology**

The annual incidence of systemic-autoimmune-disease-associated PAH has been estimated to be between one and three cases per million population, with a prevalence ranging from 5 to 15 cases per million. Cohort studies have reported that PAH prevalence in SLE varies widely between 0.5% and 43%, although more recent reports estimate this as being between 0.5% and 17.5%. Other investigators estimated the prevalence of PAH to be 14% based on the first transthoracic echocardiogram (TTE) of lupus patients. The differences in prevalence of PAH to be 14% based on the first transthoracic echocardiogram (TTE) of lupus patients.10 The differences are mainly attributed to the method used for diagnosis (TTE vs right heart catheterization, RHC), the threshold for PAH (right ventricular systolic pressure, RVSP >30 mmHg or >40 mmHg), and the studied population.

The majority of patients with SLE-PAH are women (95% in the REVEAL registry with RHC confirmed disease) with a mean age of 45 years (45.5±11.9) at PAH diagnosis. In rare cases, PAH is the first manifestation leading to SLE diagnosis. Concerning severity, this is usually moderate with pulmonary artery systolic pressure (PASP) ranging between 40 and 60 mmHg and PVR between 5 and 15 Wood units.

**Predictive factors**

Certain lupus manifestations and immunologic abnormalities have been identified as predictors of PAH in observational cohort studies. In this context, Raynaud’s phenomenon, active renal disease, and vasculitic manifestations (digital gangrene, cutaneous vasculitis, and livedo reticularis) were shown to independently predict PAH development. In another small prospective study with 34 patients, Raynaud’s phenomenon was strongly related to increased PASP as assessed by TTE. Pleural effusions were also demonstrated to occur with higher frequency in CTD-associated PAH; patients with pleural effusions had higher mean right atrial pressure (mRAP) and lower cardiac output. However, most patients in that study had overt right heart failure, which may have contributed to pleural effusion. In a recent analysis of a large Chinese cohort (n=1,934, 74 patients with PAH), pleuritis was an independent predictor of PAH in lupus and showed an odds ratio (OR) = 3.06 (95% confidence interval [CI] = 1.6–5.85). Additional clinical manifestations with an independent predictive ability for PAH were interstitial lung disease (OR = 17, 95% CI = 3.6–80) and pericardial effusion (OR = 21.3, 95% CI = 4.1–110.6). In the same study, it was shown that, paradoxically, lupus patients with PAH had less severe disease, as assessed by the SLE Disease Activity Index (SLEDAI); actually, a SLEDAI ≤9 was strongly predictive of PAH with an OR =26.4 (95% CI = 6.6–105.5). Moreover, the lack of acute rash and low erythrocyte sedimentation rate (≤20 mm/h) were also independent predictors. The clinical significance of these findings is difficult to interpret since it is believed that systemic inflammation drives PAH in these patients.

Immunological variables associated with PAH in lupus patients include positive anti-U1-RNP (ribonuclear protein) and antiphospholipid antibodies. Anti-U1-RNP antibodies, in particular, were strong predictors for PAH in several studies with a hazard ratio ranging from 2.6 to 12.4 (95% CI =3.6–42.9). Antiphospholipid antibodies, mainly anticardiolipin antibodies and lupus anticoagulant, were also associated with increased risk for PAH. Anti-Sjogren’s Syndrome related antigen A antibodies were demonstrated as strong predictors with an OR =4.8 (95% CI =1.7–14). Details on the predictive factors for PAH in lupus patients are given in Table 1.

**Pathogenesis**

The pathogenetic mechanisms in SLE-PAH have not been elucidated yet. However, accumulating evidence suggests...
that multiple factors, such as genetic predisposition, environmental stimuli, and immune system dysfunction play a significant role. The net result is an imbalance between vasoconstrictive and vasodilating soluble mediators, which leads to vasoconstriction with increased PVR. Endothelin-1 (ET-1) and thromboxane A2 (TXA-2) are the main mediators that lead to vasoconstriction; their serum levels were significantly elevated in patients with SLE-P AH and correlated with PAH severity. In addition, about 42% of patients with SLE-P AH were found to have antibodies against the endothelin receptor type A; their titers correlated strongly with P AH severity. These antibodies promote endothelial dysfunction and probably contribute to the inhibition of prostacyclin production by endothelial cells, which is one of the main vasodilators. In line with the vasoconstriction theory, it was recently demonstrated that lupus patients with PAH have increased arterial stiffness (assessed by brachial–ankle pulse wave velocity), and this was an independent predictor of PAH. Vasoconstriction represents an early event in the PAH pathogenic cascade, and vasoresponders (patients with a >10 mmHg decrease in PASP upon inhalation of vasoactive compounds during RHC) have a good response to calcium channel blockers, regardless of PAH etiology.

Pulmonary vasoconstriction will lead to decreased oxygen saturation and hyperexpression of the hypoxia-inducible factor (HIF) and erythropoietin (EPO), which may promote smooth muscle cell proliferation and extensive vascular remodeling. Several distinct pathways are implicated in vascular remodeling such as impaired apoptosis with upregulation of antiapoptotic proteins and abnormal proliferation of endothelial and adventitial cells. In parallel, the inflammatory response will drive the accumulation of monocytes, neutrophils, mast cells, and dendritic cells into the elastic lamina, which in turn induce the production of certain chemokines, cytokines, and growth factors that perpetuate abnormal remodeling. In later stages of PAH, microthrombi in the pulmonary vasculature will lead to further elevation of PASP.

In the aforementioned pathogenetic model of PAH, many characteristics of SLE, such as vasculitis, thrombosis, and interstitial pulmonary fibrosis are implicated. Pulmonary vasculitis is mediated through immune complexes; both immunoglobulins and complement have been demonstrated to deposit on the arterial wall. Other pulmonary vascular pathologic findings were similar to those of idiopathic PAH and mainly consisted of plexiform lesions, smooth muscle cell hypertrophy, intimal proliferation, and collagen deposition. In addition, CTD-associated PAH was characterized by more frequent involvement of pulmonary veins and perivascular inflammatory infiltration. Thrombosis occurs more frequently in lupus patients, particularly in the presence of antiphospholipid antibodies. Although antiphospholipid syndrome per se may lead to chronic thromboembolic pulmonary hypertension, antiphospholipid antibodies have been shown to mediate endothelial dysfunction and induce the secretion of adhesion molecules. This may also occur in the presence of anti-endothelial cell antibodies — their binding to endothelial cells results in increased production of IL-6 and IL-8. The role of other immunological abnormalities in SLE-P AH, such as the decreased numbers of T regulatory cells and the more frequent presence of the anti-U1-RNP antibodies, has not been clarified yet. A schematic representation of the pathogenesis of PAH in the context of SLE is presented in Figure 1.

Clinical presentation and diagnosis

Dyspnea (initially exertional), dry cough, chest pain, exercise intolerance, and fatigue are the cardinal clinical manifestations of PAH. Physical findings may include elevated jugular venous pressure, accentuated S2 cardiac sound, and murmurs indicative of tricuspid and/or pulmonic valve insufficiency. In late stages, right heart failure with liver enlargement due to congestion, ascites, and/or lower limb edema may be seen.

The gold standard for PAH diagnosis is RHC, which precisely assesses PASP, diastolic PAP, PCWP, PVR, and cardiac output. Secure diagnosis requires a mean PAP ≥25 mmHg at rest. Documentation of all these parameters also allows for rough etiologic characterization of PAH; a PCWP ≤15 mmHg is required to exclude cases of heart failure. However, it was shown that many patients with heart failure and preserved ejection fraction have low PCWP (16–18 mmHg). PVR ≥3 Wood units should also be included in the characterization of PAH. During the procedure, vasoreactivity can be assessed with the use of nitric oxide, epoprostenol, or adenosine. Most SLE patients are not vasoreactive, and therapy with calcium channel blockers has not proven to be beneficial. RHC is not always feasible due to availability and/or procedure-related complications (mild-to-moderate in 1.1%, mortality 0.055%).

TTE can provide a reliable estimation of the RVSP and tricuspid valve insufficiency. RVSP is calculated by the modified Bernoulli equation as RVSP =4v² + mRAP, where v equals the tricuspid regurgitant jet velocity (a reflection of the right ventricular-to-atrial systolic pressure gradient).
and mRAP is estimated from the diameter and respiro-
phasic variability of the inferior vena cava during normal
respiration.\textsuperscript{37} RVSP does not necessarily correlate with the
measurement of PASP as obtained with RHC.\textsuperscript{38} In that study,
TTE and RHC provided comparable measurements of PASP
(77.2±35 mmHg vs 76.9±21.7 mmHg, respectively). How-
ever, TTE was inaccurate (over- or underestimating PASP by
>10 mmHg) in 57% of the cases. Other studies showed that
the correlation between TTE and RHC was satisfactory, at
least for the initial evaluation of such patients.\textsuperscript{39} Moreover,
it was recently demonstrated that two consecutive TTEs
with an RVSP ≥40 mmHg were the most accurate predic-
tors for PAH with a sensitivity of 100%, specificity 97%,
positive predictive value of 70%, and negative predictive
value of 100%.\textsuperscript{40} In general, TTE is recommended for the
initial screening of patients with suspected PAH as well
as for the evaluation of response to treatment.\textsuperscript{34} Of note,
TTE may lead to PAH diagnosis in asymptomatic patients,
although the threshold used in that study was rather low
(RVSP =30 mmHg).\textsuperscript{41}

Additional investigations are warranted for the precise
etiologic diagnosis of PAH. High-resolution computed
tomography of the thorax will help exclude any concomitant
interstitial lung disease, while ventilation/perfusion scan
for acute or chronic thromboemboli will rule out chronic
thomboembolic pulmonary hypertension.\textsuperscript{15,34} Rare causes of
PAH such as sleep apnea syndrome (assessed by polysom-
nography), human immunodeficiency virus, schistosomiasis,
and portopulmonary hypertension should also be excluded.
Pulmonary function tests reveal isolated decreased diffusing
capacity for carbon monoxide ($D_{LCO}$).

**Therapeutic approach**

Treatment of SLE-PAH should be prompt and aim at PASP
normalization in order to maximize survival. Thorough diag-
nostic evaluation is of utmost importance since patients with
no other risk factors (eg, left heart failure, chronic thromboembolic PAH) should be treated accordingly (diuretics, anticoagulants, etc). Existing randomized controlled trials have solely assessed the effect of PAH-targeted therapies with endothelin receptor antagonists (bosentan), phosphodiesterase type 5 inhibitors (PDE5 inhibitors, sildenafil), and vasodilators (treprostinil, a synthetic analog of prostacyclin, PG12). In these studies, patients with different CTDs, mainly mixed connective tissue disease (MCTD) and systemic scleroderma, were also included, and a subanalysis of the lupus patients was not performed.

Additional data come from observational cohort studies using immunosuppressive therapies that have shown a considerable benefit in such patients. Tanaka et al reported a significant reduction of RVSP in seven out of eight patients who received corticosteroids (starting at 500 mg/month to 1,000 mg/m²/month) were also administered in five cohort studies in conjunction with prednisone (0.5–1 mg/kg/day with slow tapering) and vasodilators or PDE5 inhibitors. Gonzalez-Lopez et al showed that CYC in combination with low doses of prednisone (<15 mg/day) was effective in 16 patients with moderate SLE-PAH as assessed by TTE. In another study with CYC, five out of 12 lupus patients responded and showed improved survival. More recent studies demonstrated that the addition of vasodilators and supportive treatment with diuretics and anticoagulants may benefit patients with more severe PAH at diagnosis; in those studies, patients with MCTD were also included. Finally, Kommireddy et al reported a mean reduction of 16 mmHg in PASP (assessed by TTE) with three intravenous CYC pulses plus oral prednisone and PDE5 inhibitors in 11/24 patients with SLE-PAH. Moreover, rituximab was shown to provide benefit in a refractory case of SLE-PAH, while another patient was successfully managed with mycophenolate mofetil and cyclosporine. Details on the studies that used immunosuppressive treatment for SLE-PAH are given in Table 2.

Other studies have used only PAH-targeted approaches in SLE-PAH. Robbins et al administered intravenous epoprostenol in six patients and observed a significant improvement in PAH hemodynamics and functional class according to the New York Heart Association. Other investigators reported similar results along with better survival in epoprostenol-treated patients. Oudiz et al showed a favorable hemodynamic response and trend toward improved quality of life in 25 lupus patients with subcutaneous treprostinil, a prostacyclin analog. Endothelin receptor antagonists, particularly bosentan, have been shown to improve functional New York Heart Association class and exercise tolerance (assessed with the 6-minute walk distance) in a randomized, placebo-controlled trial, which included 16 lupus patients, as well as other small observational studies. Moreover, sildenafil in low doses improved PAH hemodynamics and functional capacity after 12 weeks of treatment; in that study, 84 patients with CTD-associated PAH (19 with SLE) were subanalyzed. Finally, a randomized, placebo-controlled trial with riociguat, a soluble guanylate cyclase stimulator with vasoactive, antifibrotic, and anti-inflammatory effects, showed favorable results in PAH associated with CTDs.

In that study, 18 patients with SLE were included; however, specific details for these patients were not provided. Details on the studies that used PAH-targeted therapies for SLE-PAH are given in Table 3.

Prognosis
PAH significantly affects survival and quality of life in CTDs. Direct comparisons from the REVEAL registry showed that patients with CTD-associated PAH had poorer 1-year survival as compared to patients with idiopathic PAH (86% vs 93%). Among the CTDs group, however, SLE patients had the best rates for 1-year survival (94% vs 82% for scleroderma and 88% for MCTD), although all patients had comparable hemodynamic characteristics at PAH diagnosis. Data from the Korean CTD-PAH registry, with 174 patients enroled, demonstrated that the 1- and 3-year survival were 90.7% and 87.3%, respectively. In that study, low DLCO, diabetes, and pleural effusion were poor prognostic factors, while anti-U1-RNP antibodies seemed to be protective. A recent meta-analysis of six studies encompassing 323 lupus patients with PAH demonstrated that the pooled 1-, 3-, and 5-year survival were 90.7% and 87.3%, respectively. Higher mPAP, PVR, and brain natriuretic peptide and lower 6-minute walk distance were related to poor survival. In an older systematic review of 23 observational studies, higher mPAP at diagnosis, Raynaud’s phenomenon, thrombocytopenia, pregnancy, pulmonary vasculitis, and anticardiolipin antibodies were associated with decreased survival.

Conclusion
PAH affects 0.5%–17.5% of patients with SLE and has significant effects on prognosis. Its pathogenesis is multifactorial and mediated through vasoconstriction, hypoxia, and impaired vascular remodeling. Immunosuppressive treatment...
Table 2 Studies with immunosuppressive medications for SLE-PAH

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>N (SLE)</th>
<th>Baseline characteristics</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Notes/side effects</th>
</tr>
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<tbody>
<tr>
<td>Tanaka et al 46</td>
<td>2002</td>
<td>12</td>
<td>Age 38.3±14.2 years</td>
<td>8/12 received corticosteroids and/or CYC</td>
<td>7/8 responded (significant decrease in RVSP). 2/7 relapsed (treated with corticosteroids plus CYC successfully)</td>
<td>Retrospective, four patients had SLE + SSc overlap syndrome. One patient died due to sepsis, one developed hemorrhagic cystitis</td>
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<tr>
<td>Gonzalez-Lopez et al 47</td>
<td>2004</td>
<td>34</td>
<td>Age 38±11 years</td>
<td>IV CYC (500 mg/m²/month × 6 months) n=16 vs enalapril 10 mg/day for 6 months, n=18 + oral prednisone &lt;15 mg/day</td>
<td>1. Significant reduction in PASP in both groups (13 mmHg for CYC, 8 mmHg for enalapril) 2. CYC performed better in moderate PAH (initial PASP &gt;35 mmHg), enalapril was not effective 3. NYHA functional class improved only with CYC</td>
<td>Randomized controlled trial, PAH defined as RVSP &gt;30 mmHg by TTE. Patients on CYC had more infections and gastrointestinal side effects</td>
</tr>
<tr>
<td>Sanchez et al 48</td>
<td>2006</td>
<td>28 (12)</td>
<td>Age 29 years mPAP 54 mmHg</td>
<td>IV CYC (600 mg/m²/month ×3 months) + oral prednisone (0.5–1 mg/kg for 4 weeks, then slow tapering)</td>
<td>IV CYC (600 mg/m²/month ×6 months) + oral prednisone (0.5–1 mg/kg for 4 weeks, then slow tapering) + VDs + supportive treatment (diuretics, anticoagulants)</td>
<td>1. Patients with less severe PAH (NYHA class I or II) may respond to IS alone 2. Patients with more severe disease may benefit from the addition of VDs</td>
</tr>
<tr>
<td>Jais et al 49</td>
<td>2008</td>
<td>23 (13)*</td>
<td>Age 31±10 years mPAP 48±12 mmHg</td>
<td>IV CYC (500 mg/m²/month ×10 months) + oral prednisone (1 mg/kg for 1 month, then tapering) + VDs (more than one could be used in a single patient)</td>
<td>1. mPAP significantly decreased from 39.5±9.1 to 28.9±11 mmHg 2. PVR: trend for decrease (700±434 to 481±418 dynes/cm²) 3. Improved long-term prognosis</td>
<td>Patients with MCTD and SSc were also included. Two of 28 patients died due to sepsis; minor side effects (leukopenia, thrombocytopenia) were infrequent.</td>
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<tr>
<td>Miyamichi-Yamamoto et al 50</td>
<td>2011</td>
<td>13 (7)</td>
<td>Age 42±8 years mPAP 39.5±9.2 mmHg</td>
<td>IV CYC (500 mg/m²/month ×3 months) + oral prednisone (0.5–1 mg/kg for 4 weeks, then slow tapering) + PDE5 inhibitors in 20/24</td>
<td>IV CYC (500–1,000 mg/m²/month ×3 months) + oral prednisone (0.5–1 mg/kg for 4 weeks, then slow tapering) + PDE5 inhibitors in 20/24</td>
<td>Analysis for 13 patients with CTDs. Among seven SLE patients, five responded quickly (in months). Two patients developed mild liver dysfunction.</td>
</tr>
<tr>
<td>Kommireddy et al 51</td>
<td>2015</td>
<td>24</td>
<td>Age 25.4±8 years mPAP 59.3±18.7 mmHg</td>
<td>IV CYC (500–1,000 mg/m²/month ×3 months) + oral prednisone (0.5–1 mg/kg for 4 weeks, then slow tapering) + PDE5 inhibitors in 20/24</td>
<td>11/24 responders PASP reduced from 59.3±18.7 to 43.3±20.9 mmHg at 6 months</td>
<td>Retrospective, PAH defined as RVSP &gt;30 mmHg by TTE. 2/24 deaths, one from resistant PAH and one from septic shock</td>
</tr>
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</table>

Note: *Within the 13 SLE patients of this study, 9 received immunosuppressive treatment and 14 vasodilators.

Abbreviations: IV, intravenous; mPAP, mean pulmonary artery pressure; SLE-PAH, SLE-associated PAH; SLE, systemic lupus erythematosus; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5 inhibitors; RVSP, right ventricular systolic pressure; CYC, cyclophosphamide; SSc, systemic sclerosis; PASP, pulmonary artery systolic pressure; mPASP, mean PASP; TTE, transthoracic echocardiogram; PVR, pulmonary vascular resistance; NYHA, New York Heart Association; IS, immunosuppressive; VD, vasodilator; 6MWD, 6-minute walk distance; MCTD, mixed connective tissue disease; WU, Woods units.
is efficacious in selected cases, while PAH-targeted therapies may provide additional benefit.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


