

# Pulmonary Hypertension in Systemic Lupus Erythematosus



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Pulmonary and cardiac manifestations (**Table 1**) are common in systemic lupus erythematosus (SLE). They occur in the vast majority of patients, and as a result, patients with SLE have a marked decrease in exercise compared with controls.<sup>1,2</sup> Although pulmonary hypertension (PH) is less frequently reported, exercise hemodynamics are abnormal in patients with SLE, with higher pulmonary artery pressures at rest and for each stage of exercise when compared with controls.<sup>2</sup> This occurs in the setting of similar cardiac indexes, which suggests that the mechanism for exercise intolerance is an increase in pulmonary vascular resistance. In addition to cardiopulmonary complications, exercise intolerance in SLE may be caused by overwhelming fatigue, physical deconditioning, peripheral neuropathy, arthralgias/arthritis, and muscle weakness, which further complicates the evaluation of dyspnea in patients with SLE.

All 5 World Health Organization (WHO) categories (**Figure 1**) of PH can be found in patients with SLE. The whole spectrum of pulmonary arterial hypertension (PAH) in SLE has also been reported, including pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis.<sup>3,4</sup> Pulmonary arterial hypertension as a consequence of noncirrhotic portal hypertension has also been reported.<sup>5,6</sup> Pulmonary venous hypertension is often seen as a result of left ventricular dysfunction from diastolic dysfunction, myocarditis, ischemic heart disease, or left ventricular valvular dysfunction secondary to Libman Sachs endocarditis. Pulmonary hypertension in SLE may be a consequence of interstitial lung disease, diaphragmatic dysfunction, and chronic thromboembolic disease. Pulmonary hypertension has also been associated with pulmonary vasculitis with or without alveolar hemorrhage.<sup>7-9</sup>

*Key Words*—Pulmonary hypertension; systemic lupus erythematosus; lupus.

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**Table 1. Cardiopulmonary Manifestations of Systemic Lupus Erythematosus**

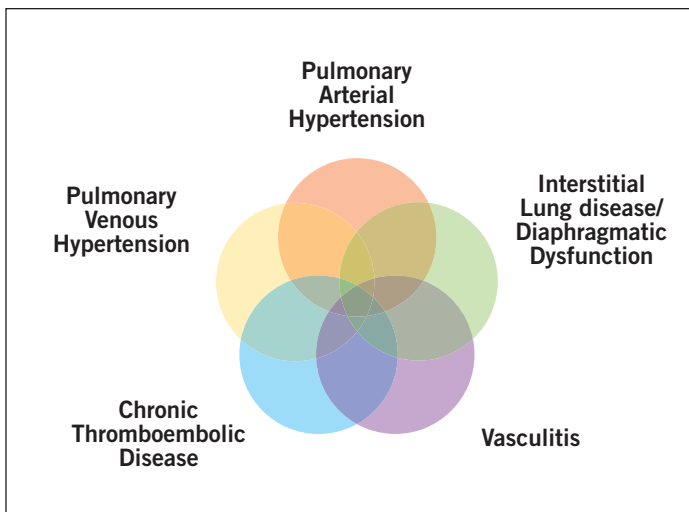
Acute lupus pneumonitis	Obstructive lung disease
Acute reversible hypoxemia	Pericardial disease
Alveolar hemorrhage	Pleural effusion
Atelectasis	Pleurisy
Coronary artery disease	Pneumothorax
Diaphragmatic dysfunction	Pulmonary embolism
Diastolic dysfunction	Pulmonary hypertension
Interstitial lung disease	Uremic pulmonary edema
Myocarditis	Valvular lesions

## Prevalence, Demographics, and Risk Factors

Studies of patients with SLE have found a prevalence of PH ranging from 0.5% to 43%, although the degree of PH is typically modest.<sup>10-16</sup> The prevalence varied based on the method used for detection, and many patients in these reports either had significant restrictive lung disease or data reported were inadequate to determine the etiology of the PH. The prevalence of comorbid SLE and PH (SLE-PH) has been shown to increase over time. In a serial study of 28 patients with SLE, the prevalence of PH measured by echocardiogram increased from 14% to 43% with 5 years of follow-up.<sup>16</sup> In an autopsy series of 20 patients with SLE, 8 (40%) patients had evidence of pulmonary vascular involvement; although clinically overt PH was present in only 1 patient.<sup>17</sup>

Clinical manifestations (**Table 2**) of SLE-PH are variable, but the predominant features include the insidious onset of shortness of breath, fatigue, and chest pain. Unfortunately, the disease process is usually far advanced with irreversible changes of the pulmonary vasculature by the time symptoms or signs develop. An isolated diffusion defect may be predictive of PH in patients with SLE.<sup>18</sup>

The characteristics of patients with SLE-PH are similar to those of patients with idiopathic pulmonary arterial hyper-



**Figure 1. Etiology of pulmonary hypertension in systemic lupus erythematosus.**

tension (IPAH), which raises the possibility of shared etiologies. Patients are predominantly women of child-bearing potential: aged from 18 to 40 years with a 10 to 1 ratio of female over male.<sup>19,20</sup> In a study that compared 20 patients with SLE-PH with 34 patients with IPAH, those with SLE-PH had a significantly shorter time from symptom onset to diagnosis and were more likely to have Raynaud phenomenon and the presence of autoantibodies.<sup>21</sup> Patients with SLE-PH were also more likely to have a pericardial effusion and were less likely to be vasoresponsive to nitric oxide during right heart catheterization. In addition, SLE-PH patients had less hypoxemia and better hemodynamics, but a significantly increased mortality risk.

Extrapulmonic manifestations can be found with IPAH including Raynaud phenomenon (30%), arthralgias, and arthritis.<sup>22-24</sup> Serologic abnormalities such as hypergammaglobulinemia, positive antinuclear antibody (ANA), rheumatoid factor, and biological false-tests for syphilis have also been reported, which suggests that some patients with IPAH may have an autoimmune disease confined to the pulmonary vasculature.<sup>22-25</sup> Alternatively, these patients may be at risk for developing an underlying connective tissue disease (CTD), such as SLE, later on in the disease course.

Study findings indicate that the duration of SLE does not correlate with the development of PH, although many patients with SLE develop PH within the first 5 years. Pulmonary hypertension may be a presenting manifestation of SLE that necessitates close follow-up of all patients newly diagnosed with IPAH.<sup>26</sup> The occurrence of PH also appears unrelated to the severity or activity of SLE such as high anti-double stranded (ds)DNA and/or grossly elevated erythrocyte sedimentation rate (ESR) and can occur when nonpulmonary disease activity is quiescent.<sup>19,20,26,27</sup> This is in contrast to a study by Simonson and colleagues<sup>13</sup> that showed that the duration of SLE and the duration of steroid therapy tended to be shorter in SLE patients with PH, although the use of anti-inflammatory agents was more common when compared to a population of SLE patients without PH. An additional study showed that PH, as recognized by right ventricular echocardiography, occurred during 288 acute flares

## Table 2. Possible Risk Factors for the Development of Pulmonary Hypertension in Systemic Lupus Erythematosus

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- Female sex
- Isolated reduction in diffusion
- Raynaud phenomenon
- Renal disease
- Digital gangrene
- Cutaneous vasculitis/livedo reticularis
- Rheumatoid factor
- Antiribonuclear protein
- Antiphospholipid antibodies
- Antiendothelial antibodies

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of SLE, which suggests that a reversible increase in pulmonary vasoconstrictor tone may be the first hemodynamic disturbance, with fixed PH developing later.<sup>28</sup>

As many as 75% of patients with SLE-PH have Raynaud phenomenon, which is higher than the expected rate of 25% among all patients with SLE.<sup>13,19,20,25,29,30</sup> Asherson and colleagues<sup>19,20</sup> have reported that 63% of patients in their study had renal disease and approximately one-third had evidence of peripheral cutaneous vasculitis, livedo reticularis, and digital gangrene.

### Autoantibodies

Patients with SLE-PH are universally positive for ANA. Antibodies to ribonuclear protein (RNP) and rheumatoid factor (RF) are often present in SLE-PH, although no pathogenic role has been postulated. Frequently, patients have antiphospholipid antibodies (aPL) and antiendothelial antibodies (aECA).<sup>10,19,20,30,31</sup> The prevalence of RNP in SLE-PH is reported in a majority of patients, which is greater than the reported prevalence of 25%, which occurs in all patients with SLE.<sup>30</sup> The prevalence of RF has been reported to be as high as 50% to 80% in SLE-PH.<sup>10,19</sup> The frequency of PH in patients with SLE and a positive aPL is considerably higher than in patients with SLE and negative aPL (83% versus 25%).<sup>30</sup>

### Pathology

Autopsy findings suggest that SLE-PH may be multifactorial in origin.<sup>25,30-32</sup> Findings include acute fibrinoid necrosis and vasculitis, as well as chronic intimal fibrosis, medial hypertrophy, alteration of elastic laminae, periadventitial fibrosis, aneurysmal dilation, and plexiform lesions, which are virtually identical to the alterations seen in patients with IPAH.<sup>9,17,29</sup> These changes occurred in arteries, arterioles, and veins. Occasional cases with thrombotic arteriopathy have also been reported and were found to correlate with a hypercoagulable status, including positive lupus anticoagulant and anticardiolipin antibodies.<sup>6,33</sup>

Acute inflammation of small pulmonary arteries and arterioles has also been found on autopsy in patients with SLE.<sup>30</sup> Deposition of circulating immune complexes (IgG and C1q) with antinuclear and anti-dsDNA activity has been

described. The presence of diffuse interstitial fibrosis in affected vessels further supports the likelihood of chronic inflammation that occurs as a result of the deposition of such complexes and/or direct injury to the vessel wall.<sup>10,34</sup>

### Pathogenesis

The causal relationship between SLE and PH has never been established. However, multiple small vessel inflammation and/or vasculitis as well as sustained vasoconstriction, in situ thrombosis, and/or thromboembolism and interstitial pulmonary fibrosis, all features of SLE, may damage and reduce the pulmonary vascular bed and lead to PH.<sup>20,35</sup>

There is an imbalance between vasoconstrictors and vasodilators in SLE-PH. Higher serum endothelin levels were found in patients with SLE-PH compared with non-PH patients with SLE and healthy controls.<sup>36</sup> There is also an imbalance of thromboxane and prostacyclin that results in endothelial dysfunction, vascular damage, and remodeling that is felt to be pathophysiologically important.<sup>37</sup> The inhibition of prostacyclin production by endothelial cells is possibly related to the action of aPL on the endothelial surface.<sup>38,39</sup> In addition, when antiphospholipid antibodies bind to the phospholipids on the endothelial surface, there is resultant in-situ thrombosis and the release of soluble mediators and subsequent vascular injury.<sup>9,37</sup>

Antiendothelial cell antibodies may also play a key pathogenic role in the development of SLE-PH. Systemic lupus erythematosus is an autoimmune disease characterized by polyclonal B cell activation. One factor that stimulates B cells to produce immunoglobulin is interleukin 6 (IL-6), and endothelial cells are an important source of IL-6. Serum titers of aECA are elevated in patients with active SLE, particularly in patients with PH, digital vasculitis, Raynaud phenomenon, or serositis. Binding of antiendothelial cell antibodies or immune complexes to endothelial cells may augment the release of IL-6 and result in vascular injury and ensuing intimal and medial proliferation and in situ thrombosis.<sup>40</sup>

The striking correlation between the occurrence of Raynaud phenomenon and SLE-PH suggests that pulmonary arterial vasospasm may also be involved in the pathogenesis of SLE-PH. Raynaud phenomenon is part of a systemic vascular response that includes a decrease in size of the pulmonary capillary bed, which may in turn result in muscular necrosis and secondary inflammation.<sup>41,42</sup> However, since the vast majority of patients with Raynaud phenomenon do not develop PH, this would suggest that other factors are operative in those who are prone to develop PH. Alternatively, in conjunction with the high prevalence of RNP found in SLE-PH, this subset of SLE patients may actually belong to the scleroderma spectrum of disease where PH is more common.

### Treatment

There are no independent consensus guidelines for the treatment of SLE-PH; instead, treatment recommendations are generalized for PAH from all causes. There are no reports of the efficacy of calcium channel blockers in patients with SLE-PH and vasoreactivity is rare.

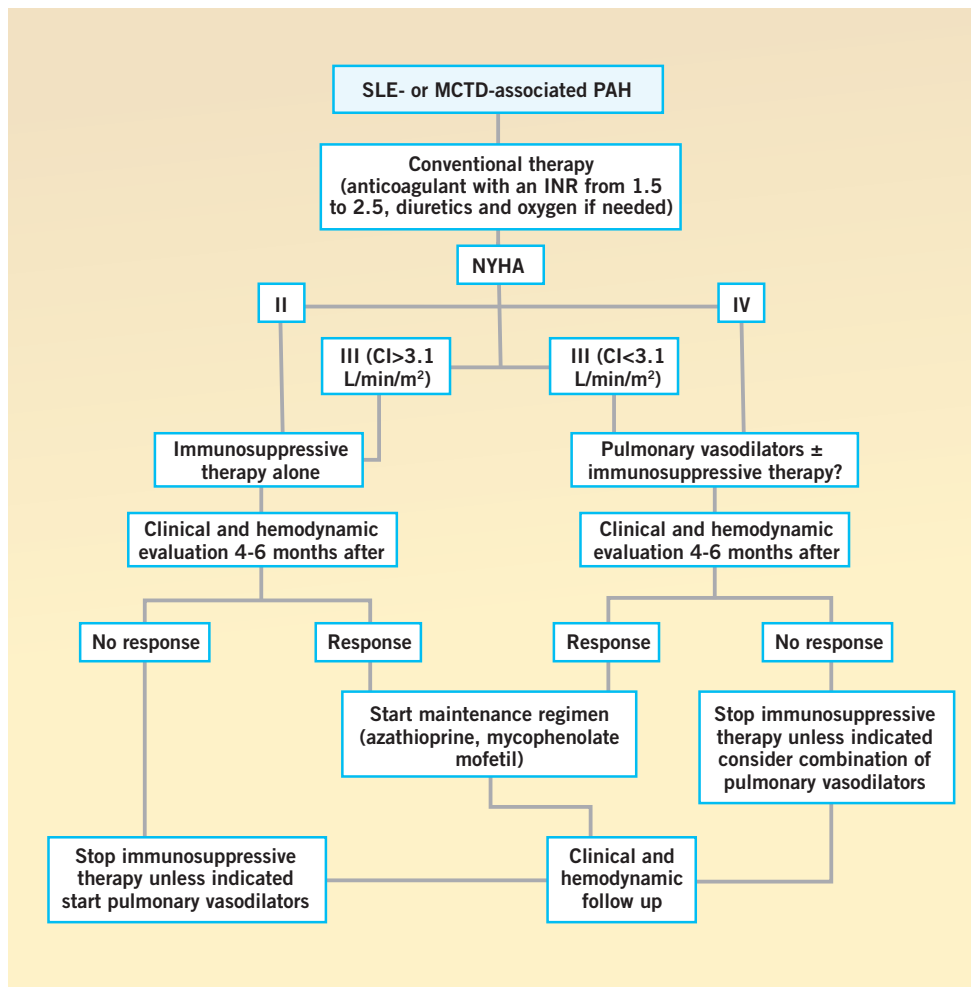
*Endothelin receptor antagonists.* Endothelin is a key pathogenic mediator of PAH secondary to CTD.<sup>43</sup> A post-hoc analysis of the CTD subgroup from the pivotal studies of bosentan and their open-label extensions included 8 patients (12%) with SLE.<sup>43</sup> Patients with PAH secondary to CTD who were treated with bosentan were stable during the 6-minute walking distance test (+19.5 m, 95% confidence interval [CI] -3.2 to 42.2), whereas patients treated with placebo deteriorated (-2.6 m, 95% CI -54.0 to 48.7). In a second small uncontrolled study composed of patients with scleroderma and SLE, long-term treatment with bosentan was effective in improving exercise capacity and pulmonary hemodynamics in patients with CTD-associated PAH.<sup>44</sup> Patients with SLE were also included in the pivotal trials for ambrisentan and sitaxsentan; the CTD subgroup analyses in these trials have yet to be published.

*Phosphodiesterase type-5 inhibitors.* Case reports have shown that sildenafil improved quality of life in patients with SLE-PH and a minority of patients with SLE was included in the pivotal trial leading to the regulatory approval of sildenafil.<sup>45,46</sup>

*Prostanoid therapy.* Treatment of PAH with intravenous epoprostenol has been shown to improve hemodynamics, exercise tolerance, functional status, and quality of life in patients with IPAH and PAH related to the scleroderma spectrum of disease and is felt to be of significant benefit in other forms of CTD. There are multiple case reports describing a benefit from epoprostenol in patients with SLE-PAH. The largest case series (n = 6) of patients with SLE showed that epoprostenol improved functional class in all patients with a dose ranging from 4 to 46 ng/kg/min.<sup>26</sup> Four of the 6 patients underwent repeat hemodynamic evaluation (9 to 16 months after starting epoprostenol) and had a  $38 \pm 21\%$  improvement in their mean pulmonary artery pressure and a  $58 \pm 12\%$  improvement in their pulmonary vascular resistance.

The adverse effects from epoprostenol did not differ from those seen in patients with IPAH, and except for one patient, there was no exacerbation of SLE. All patients were treated with anticoagulation; nevertheless, one patient with aPL developed a right subclavian and jugular vein thrombosis that required removal of a Hickman catheter and subsequently severe thrombocytopenia developed. Severe refractory thrombocytopenia has been reported in a second case series of patients with SLE-PH.<sup>47</sup>

A subgroup analysis of 2 multicenter, randomized double-blind placebo-controlled prospective trials of treprostinil versus placebo in 470 patients with PAH included 90 patients with CTD, 25 (28%) of whom had SLE.<sup>48</sup> There were no statistically significant differences in pretreatment and posttreatment hemodynamic variables between patients with different CTDs. Modest statistically significant improvements were seen in cardiac index and pulmonary vascular resistance. After 12 weeks, the placebo-corrected median improvement from baseline in the 6-minute walking distance test was 25 m in treprostinil-treated patients ( $P = .055$ ); this improvement appeared to be dose related. Dyspnea-fatigue scores also improved in the treprostinil group compared with the placebo group ( $P = .014$ ). Adverse effects included infusion site pain and typical side effects



**Figure 2. Proposed algorithm for treatment of patients with PAH associated with SLE or MCTD.** Responders to immunosuppressive therapy were defined as patients in NYHA functional class 1 or 2 with hemodynamic improvement after the last pulse of cyclophosphamide. This algorithm must be read with caution because it relies on retrospective and open-label data and must therefore be confirmed by future randomized controlled trials. CI, cardiac index; INR, international normalized ratio; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; NYHA, New York Heart Association; SLE, systemic lupus erythematosus. Copyright © 2008 American College of Rheumatology. Reprinted with permission from Jais et al.<sup>55</sup>

related to prostaglandins, and were tolerated by most patients.

Seventeen percent of subjects had CTD-associated PAH in the pivotal trial for inhaled iloprost, including a minority of patients with SLE-PAH.<sup>49</sup>

**Immunosuppressive therapy.** It is currently accepted that immune and/or inflammatory mechanisms contribute to PAH genesis or progression, especially in patients with CTD. Inflammatory cell infiltrates composed of macrophages and lymphocytes have been detected in plexiform lesions from patients with CTD-associated PAH. In addition, ANA, rheumatoid factor, IgG, and complement have been identified in the pulmonary vessel walls of the patients.<sup>50</sup> There are anecdotal reports of improvement in SLE-PH with corticosteroids, although corticosteroids alone are rarely sufficient.<sup>51-53</sup> There are also multiple case-reports and small case series of improvement in SLE-PH with immunosuppressive therapy, which suggests that a small subset of patients have more of a vasculitic as opposed to a vasculopathic phenotype.<sup>54-56</sup> Although most studies have shown no

benefit in SLE-PAH without the addition of PAH specific therapy, these case-reports support aggressive control of the underlying SLE in addition to treatment of the PAH.

In the largest case series, 23 consecutive patients with SLE or mixed connective tissue disease-associated PH were treated with first-line immunosuppressive therapy (600 mg/m<sup>2</sup> cyclophosphamide intravenously monthly for 6 months and oral prednisone 0.5-1 mg/kg/d for 4 weeks) either alone (n = 16) or in combination with vasodilators (n = 7).<sup>55</sup> Fifty percent of the patients in the first line immunosuppressive therapy alone group had a significantly improved WHO functional class, 6-minute walking distance test, and mean pulmonary artery pressure. Patients in WHO functional class I or II and/or with a cardiac index greater than 3.1 L/m/m<sup>2</sup> at baseline and a pulmonary vascular resistance less than 6.6 mmHg/L/min were more likely to respond to immunosuppressive therapy. There was also a trend for responders to have anti-dsDNA and anti-Sm antibodies. Although this was not significant, SLE activity was higher in the responders than in the nonresponders. Among the 8 patients who responded to the immunosuppressive therapy alone, 5 had a stable clinical and hemodynamic status and were alive after a mean follow-up of 47 ± 30 months after the last pulse of cyclophosphamide. Three patients had a relapse after the last pulse of

cyclophosphamide and required further immunosuppressive therapy.

This relatively high frequency of relapses raises the issue of the need for an immunosuppressive maintenance regimen similar to that recommended for other serious visceral involvement such as nephritis. For patients with more severe disease, combination therapy with immunosuppressants and PAH-specific therapy was more effective, although the exact role of immunosuppressive therapy in this combination is not known (**Figure 2**). It remains to be demonstrated, in a large randomized placebo-controlled trial, whether adding immunosuppressive therapy to vasodilators at diagnosis would provide additional benefits to patients with SLE-PH.

**Pregnancy.** It is dangerous for women with active SLE to be pregnant. Pregnancy can exacerbate underlying SLE and is an absolute contraindication in patients with PAH.<sup>57</sup> Experts suggest that consideration should be given to screening all pregnant women with SLE and women with SLE who are planning on conceiving, given the seriousness

of SLE-PH.<sup>58,59</sup> The maternal mortality secondary to SLE-PH has been reported to be 66%, which is higher than the 56% mortality that has been reported in a systematic review of pulmonary vascular disease in pregnancy.<sup>60,61</sup>

**Transplantation.** Patients with multisystem involvement from CTD are generally excluded from consideration from heart-lung and lung transplantation because of profound donor organ shortages and complications of comorbidities as a result of systemic disease. However, heart-lung and lung transplantation for PAH has resulted in long-term survival in patients with SLE.<sup>62,63</sup> This is consistent with the favorable outcomes that can be expected after renal transplantation, an organ that is frequently transplanted in patients with SLE.<sup>62</sup>

### Survival

Death due to PH is rare in several western series of SLE patients, accounting for less than 1% to 15.7% of the total, and PH is often unrecognized for a long period of time in those patients who eventually die from it. This is in contrast to SLE patients in Korea, where PH is the third leading cause of death in SLE patients.<sup>64</sup> The overall mortality rate of SLE-PH is 25% to 50% at 2 years after PH is diagnosed, although these studies are largely from the pretreatment era.<sup>11,13,14,35,36,56,65</sup> Even with improved mortality in today's treatment era, SLE-PH has a worse prognosis than IPAH.

### Conclusion

Pulmonary and cardiac manifestations are common in SLE, and all 5 WHO categories of PH can be found in patients with SLE. Since there is no relationship between the severity or duration of SLE and the development of pulmonary hypertension, the association of these 2 conditions should be kept in mind by all clinicians who treat these patients. PAH can be a presenting manifestation of SLE, so patients with newly diagnosed IPAH need to be carefully evaluated for the development SLE. Consideration should be given to screening SLE patients with Raynaud phenomenon, positive aPL, RNP, RF, aECA, or those considering pregnancy. In patients with SLE-PH, experts suggest that the underlying SLE should be aggressively treated with immunosuppressive therapy in addition to PAH-specific therapies. ■

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# Pulmonary Hypertension and the Antiphospholipid Syndrome



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Antiphospholipid antibodies (aPL) have been implicated in the development of both idiopathic pulmonary arterial hypertension (PAH) and PAH associated with connective tissue disease (CTD) and chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary venous hypertension (PVH) can also develop as a sequela of aPL-associated valvular heart disease (Libman-Sacks endocarditis).

Antiphospholipid antibodies are a group of autoantibodies with an apparent specificity for anionic phospholipids. In the clinical laboratory, aPL are typically detected in anticardiolipin assays and by their ability to prolong coagulation tests in lupus anticoagulant assays. Most aPL are directed against certain phospholipid-binding plasma proteins rather than phospholipids. The best characterized antigenic targets are b<sub>2</sub>-glycoprotein I (b2GPI) and prothrombin. Anti-b2GPI antibodies are detected in anticardiolipin assays. Lupus anticoagulant assays detect certain anti-b2GPI antibodies as well as antiprothrombin antibodies. Immunoassays using purified b2GPI as the antigen are also available, and antiprothrombin immunoassays have recently been developed.

## The Antiphospholipid Syndrome

The antiphospholipid syndrome (APS) is the association of persistent aPL with arterial or venous thrombosis and/or recurrent pregnancy losses. Other clinical features associated, or possibly associated with aPL, include a form of valvular heart disease (Libman-Sacks endocarditis), livedo reticularis, and certain nonstroke neurological problems. International consensus criteria for the classification of definite APS were proposed in 1999 and updated in 2005.<sup>1,2</sup> Antiphospholipid syndrome can occur in association with systemic lupus erythematosus (SLE), or related conditions (secondary APS), or in the absence of other autoimmune disease (primary APS).

*Key Words*—Pulmonary hypertension; antiphospholipid syndrome; chronic thromboembolic pulmonary hypertension; systemic lupus erythematosus.

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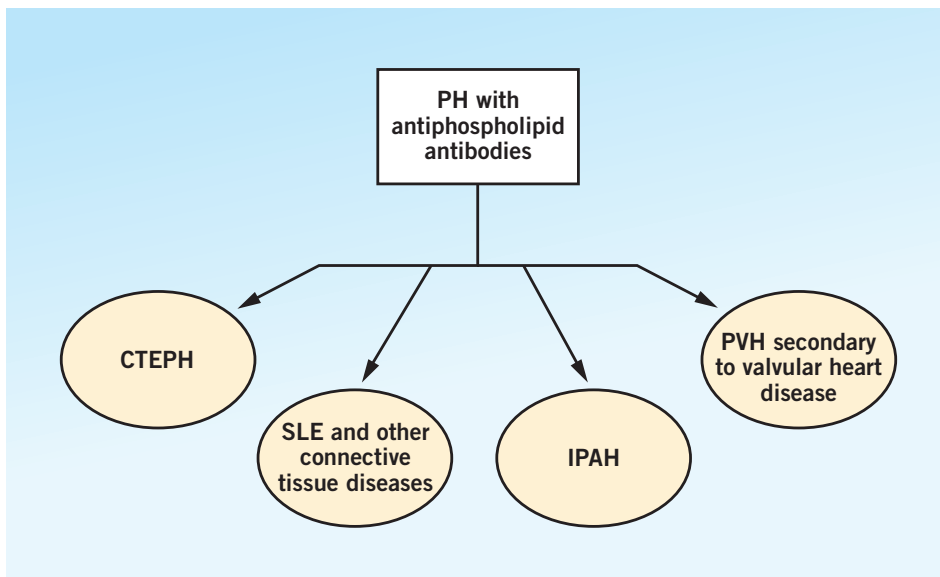
## Antiphospholipid Antibodies and Pulmonary Hypertension

Antiphospholipid antibodies have been detected in the plasma of patients with PH in 4 general settings (**Figure**): (1) patients with APS may have one or more pulmonary emboli leading to CTEPH; (2) aPL have been detected in patients with PAH associated with SLE, scleroderma, and other CTDs, in the absence of a history of venous thromboembolism; (3) aPL have been detected in some patients with idiopathic PAH (IPAH); and (4) aPL are associated with Libman-Sacks endocarditis and left-sided valvular disease can lead to pulmonary venous hypertension.

## Chronic Thromboembolic Pulmonary Arterial Hypertension

Pulmonary hypertension is an infrequent albeit feared complication of pulmonary embolism (PE). Pulmonary hypertension associated with thrombosis of the pulmonary vasculature, referred to as CTEPH, is classified as a unique entity in the Venice classification of PH (class IV).<sup>3</sup> Until recently, this was believed to be a rare complication that occurred in less than 1% of patients with PE.<sup>4,5</sup> Newer data suggest that CTEPH may be present in up to 4% to 5% of patients following PE.<sup>6,7</sup> Given the number of patients with undiagnosed and/or asymptomatic PE, the true incidence of CTEPH may be higher than these estimates. CTEPH can occur from months to many years following the initial thromboembolic event, and the natural history of the disease is poorly understood until the time the patient develops symptoms. Similar to PAH, untreated CTEPH has a uniformly poor prognosis that correlates with the extent of PH.

*Antiphospholipid syndrome.* Antiphospholipid syndrome is the most common acquired cause of venous thromboembolism (VTE) and accounts for 15% to 20% of VTE in the United States. While there are case reports on the development of CTEPH in patients with APS, good systematic studies with significant numbers of patients are lacking. The lack of data is probably due to the low incidence of CTEPH in patients with PE, as discussed above, and the long lag period between occurrence of PE and the subsequent development of CTEPH.



**Figure. Antiphospholipid antibody associated PH. The different scenarios in which aPL have been reported in PH.**

A European study of 114 patients with APS found the prevalence of PH to be 3.5% in primary APS and 1.8% in secondary APS.<sup>8</sup> Interestingly, Wolf and colleagues<sup>9</sup> observed aPL in 20% of patients with CTEPH. These data are consistent with the estimated frequency of APS as a common acquired cause of VTE and do not necessarily suggest that patients with PE due to APS are more likely to develop CTEPH than patients with PE related to other hypercoagulable conditions.

**Pathophysiology.** The pathophysiology of CTEPH is unlikely to be related solely to pulmonary artery occlusion from VTE, as the vast majority of the thrombi resolve within a few weeks of the acute event.<sup>10</sup> It has been postulated that VTE is the inciting event following which pulmonary vascular remodeling occurs over time, which results in the development of PH.<sup>11</sup> In addition, *in situ* thrombosis in the pulmonary vasculature is also well described. These thrombi are histologically indistinguishable from thromboemboli. Whether genetic and environmental factors influence the development of *in situ* pulmonary arterial thrombi or affect the resolution of emboli and thereby confer a susceptibility to development of CTEPH is not known. A causative role for aPL in the development of CTEPH has not been established, although a number of other risk factors for CTEPH have been identified, such as splenectomy and chronic inflammatory/infectious conditions.<sup>12</sup>

**Clinical manifestations.** The clinical manifestations of CTEPH are similar to those of PH of any etiology and include progressive dyspnea with exertion, decreased exercise tolerance, and fatigue. As the disease progresses, patients eventually develop evidence of right heart failure such as edema and ascites. A unique but rare finding in patients with CTEPH is the presence of bruits over the peripheral lung fields in the lower lobes.<sup>13</sup> These have been reported in up to 10% of patients with CTEPH.<sup>11</sup> It is important to realize that a history of VTE is a poor screening tool for CTEPH because the majority of patients with CTEPH do not report a

history of symptomatic VTE.<sup>10</sup> Therefore, CTEPH should be considered in the evaluation of all patients in whom PH is suspected.

**Diagnostic imaging.** Diagnostic imaging for these patients includes echocardiography, ventilation and perfusion scans (V/Q scan) or computed tomography angiogram, and pulmonary angiography, which remains the gold standard for the diagnosis of CTEPH. The observed relatively high prevalence of aPL in CTEPH, as discussed above, supports testing for these antibodies as part of the evaluation. However, it is unclear whether the diagnosis of APS would significantly alter management of CTEPH *per se* (as discussed below). The presence of aPL may be helpful in calling the physician's attention to other manifestations of APS and in the evaluation of comorbid conditions, overall risk assessment,

and patient education. There is no evidence for an increased prevalence of inherited thrombophilias in patients with CTEPH.<sup>9,14</sup>

**Treatment.** Treatment of CTEPH differs significantly from that of other forms of PH in that there is a well-defined role for anticoagulation and pulmonary endarterectomy (PEA), which is the treatment of choice. Lifelong anticoagulation is recommended for all patients with CTEPH in order to prevent recurrent VTE and progressive PH. Vitamin K antagonists (eg, warfarin) are used for anticoagulation with the goal of maintaining a therapeutic International Normalized Ratio (INR) between 2 and 3. While baseline prolongation of the INR has been reported in patients with aPL, this is rare. When there is concern over the reliability of INR for monitoring anticoagulation, alternative approaches such as measuring factor II activity or chromogenic factor X activity may be used concurrently to assess the accuracy of INR measurements.<sup>15</sup>

The use of unfractionated or low molecular weight heparins for long-term anticoagulation is not routinely recommended except in patients with recurrent thromboembolism while taking therapeutic warfarin. Pulmonary endarterectomy significantly improves symptoms and cardiopulmonary hemodynamics in these patients.<sup>16,17</sup> The exact stage of the disease at which PEA should be performed is unclear.

Surgery early in the course of the disease is recommended as there appears to be a correlation between preoperative pulmonary vascular resistance and perioperative mortality.<sup>18</sup> In addition, the degree of residual PH after surgery is a strong predictor of mortality and it has been proposed that PEA should be considered only if a significant improvement in pulmonary vascular resistance (> 50%) is expected following surgery.<sup>16</sup>

The benefit of placing inferior vena cava filters prior to PEA has not been established. While this is routinely performed at certain centers, this practice has not been univer-

sally adopted. Patients that are ineligible for surgery have been treated with prostanoids, phosphodiesterase 5 inhibitors, and endothelin receptor antagonists with variable success. Finally, there are case reports of significant benefit with use of prednisone in patients with APS and CTEPH, which may reflect an immune component of the pathophysiology in at least the subset of patients with CTEPH and aPL or APS.<sup>19,20</sup>

### **Pulmonary Hypertension Associated With Connective Tissue Disease**

Antiphospholipid antibodies are commonly present in patients with SLE and other CTDs. Development of PAH has been reported in these patients.<sup>21-24</sup> The prevalence of aPL in patients with SLE and scleroderma is 30% to 50% and about 7%, respectively.<sup>25</sup> In the majority of cases these patients do not have APS based on current criteria. Pulmonary arterial hypertension is part of the spectrum of these diseases, and a role for aPL in the pathogenesis of PAH in these conditions has not been established.

The clinical manifestations of PAH in these patients are similar to and indistinguishable from those seen with IPAH and PAH secondary to other causes. In general, the diagnostic evaluation and management of PAH in these patients is also similar to other forms of PAH. Because the primary disorders in this subgroup are immunological, the addition of immunosuppressive agents to the therapeutic regimen may be of benefit. It is important to consider CTEPH in all patients with CTDs and PH as the management of CTEPH is significantly different from other forms of PH, as discussed above.

### **Idiopathic Pulmonary Arterial Hypertension**

IPAH (previously termed primary pulmonary hypertension) is defined as the development of PAH in the absence of any other associated disease or cause. Antiphospholipid antibodies have been reported in these patients as well.<sup>26</sup> Once again, no data are available to demonstrate a causative role for these antibodies, although such a role has been speculated. Proposed mechanisms by which aPL lead to the development of IPAH include platelet and endothelial activation, which leads to pulmonary vascular remodeling and PAH. Increased levels of endothelin-1, a potent vasoconstrictor, have been demonstrated in patients with PAH and it is widely believed that endothelin-1 plays a role in the pathogenesis of PAH.<sup>27</sup> Increased levels of circulating endothelin-1 have been reported in patients with aPL and this has been proposed as a mechanism for the development of PAH in patients with aPL with or without thrombosis.<sup>28</sup>

### **Pulmonary Venous Hypertension Associated With Valvular Heart Disease**

Valvular heart disease is a well-recognized cardiac manifestation in APS and SLE. The classic abnormality is the presence of verrucous vegetations on the valve leaflets first described by Libman and Sacks.<sup>29</sup> This is variably referred to as Libman-Sacks endocarditis, verrucous endocarditis, or nonbacterial endocarditis. While reports on the incidence of Libman-Sacks endocarditis vary widely, it is conservatively

estimated to be present in about 20% to 30% of patients with SLE and about a third of patients with primary APS.<sup>30-33</sup> There are reports of an increased incidence of valvular heart disease in patients with aCL, with or without coexisting CTD.<sup>32,34</sup> Libman-Sacks endocarditis commonly involves the mitral and aortic valves and can result in significant regurgitation and eventually result in PVH. The exact incidence of PVH in patients with Libman-Sacks endocarditis is not known. Treatment with anticoagulation or antiplatelet agents does not improve the valvular disease in these patients.<sup>35-37</sup> Whether there is a role for immunosuppression in these patients is unclear as there are conflicting reports in the literature.<sup>38,39</sup>

### **Key Points**

- There is significant overlap between the different subsets of PH. Indeed, patients with IPAH or PAH in the setting of SLE can subsequently develop in situ pulmonary arterial thrombosis, which further complicates this issue.
- Although aPL are associated with venous thromboembolism, it is not clear that they play any role in the pathogenesis of PH per se.
- It is essential to identify patients with CTEPH as the therapeutic approach includes pulmonary endarterectomy, which significantly improves the prognosis and quality of life in these patients.
- The presence of aPL in patients with PAH secondary to CTD or apparent IPAH should prompt evaluation for CTEPH.
- The role of immune suppression in patients with aPL-associated PH should be evaluated prospectively. ■

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# Scleroderma Associated Pulmonary Hypertension



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With the introduction of angiotensin-converting enzyme inhibitors as an effective therapy for scleroderma renal crisis, pulmonary hypertension is now one of the leading causes of scleroderma-related deaths.<sup>1</sup> In this review, we will summarize the current evidence to support screening for scleroderma-associated pulmonary hypertension (SScPH), and we will review the available therapies for SScPH.

## Epidemiology

Estimates of the prevalence of SScPH vary, depending on the population studied and whether echocardiogram or catheterization criteria are used for the diagnosis. A recent longitudinal 4-year follow-up study of 794 patients with scleroderma who had been referred to a tertiary referral center in the United Kingdom identified a prevalence of 12% using right heart catheterization for diagnosis.<sup>2</sup> It has been postulated that such studies may underestimate the true prevalence of SScPH, since only clinically severe and symptomatic patients are referred to university centers. The UNCOVER study was a multicenter study of 50 community rheumatology practices in the United States, which evaluated patients with scleroderma and mixed connective tissue disease. Using doppler echocardiography the study found a prevalence of 26.7% for pulmonary hypertension (PH).<sup>3</sup> Furthermore, in patients with limited scleroderma who die from scleroderma-related complications, PH is the cause of death in up to 50% of patients.

Before the introduction of current therapies, PH had the worst prognosis of all scleroderma organ involvements, with a 2-year cumulative survival rate of 50% and limited survival beyond 5 years.<sup>4</sup> Earlier studies found that despite similar hemodynamics SScPH carries a higher risk of death than idiopathic pulmonary arterial hypertension (IPAH), and, in most of the available clinical trials, SScPH patients had a less robust clinical response (as measured by the 6-minute

*Key Words*—Scleroderma; pulmonary hypertension; idiopathic pulmonary arterial hypertension; antibodies.

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## Table 1. Risk Factors for Developing Isolated SScPH

Limited scleroderma
Long history of Raynaud phenomenon
Low DLCO (typically with normal FVC and minimal fibrosis)
FVC/DLCO ratio >1.6
Nucleolar ANA
U3-RNP antibody
DLCO, carbon monoxide diffusing capacity; FVC, forced vital capacity; ANA, antinuclear antibody.

walk test) than patients with IPAH.<sup>5,6</sup> With the introduction of newer therapies for PH, the prognosis for SScPH has improved compared with historical controls.<sup>7</sup> Mukerjee and colleagues<sup>2</sup> found that the 148 patients with SScPH in their cohort who received treatment had a 56% three-year survival rate, which was comparable to cohorts with IPAH.

## Risk Factors for SScPH

The mechanisms by which scleroderma patients develop PH vary depending on the underlying scleroderma phenotype (Table 1). In limited scleroderma, a primary vasculopathy develops late in the course of the disease, without any interstitial lung disease or fibrosis. In patients with diffuse scleroderma, longstanding fibrosis and chronic hypoxia can lead to secondary PH. A subgroup of patients with scleroderma had moderate pulmonary fibrosis but developed PH out of proportion to the degree of fibrosis.<sup>8</sup> Finally, findings indicate that some patients with scleroderma develop diastolic dysfunction, which may be confounded with PH.

A retrospective case-control study evaluating the patients in the Pittsburgh Scleroderma Databank who developed isolated PH found that a decreasing carbon monoxide diffusing capacity (DLCO) was a predictor of the subsequent development of PH.<sup>4</sup> Patients with PH had a mean DLCO of 52% predicted an average of 4.5 years before diagnosis of SScPH, whereas subjects who did not develop pulmonary

**Table 2. Organ Involvement in Patients With Scleroderma Specific Autoantibodies<sup>9</sup>**

Autoantibody	Clinical Association	Antibody Positive Patients (%)
Anticentromere (antinuclear antibody)	Limited scleroderma	95
	Joint involvement	60
	Digital ulcers	61
	Calcinosis	46
	Acroosteolysis	27
	Gangrene	18
	Isolated pulmonary hypertension*	19
Antitopoisomerase (Scl-70)	Diffuse scleroderma	71
	Joint involvement	86
	Tendon rubs	50
	Digital ulcers	63
	Acroosteolysis	28
	Severe pulmonary fibrosis*	23
	Cardiac disease	16
	Gangrene	13
Renal crisis	10	
U1RNP	Joint involvement	94
	Muscle inflammation	27
	Severe pulmonary fibrosis*	22
	Severe gastrointestinal involvement	14
RNA polymerase-3	Joint involvement	88
	Carpal tunnel	43
	Tendon rubs	61
	Diffuse scleroderma	85
	Renal crisis	28
Antinucleolar antibodies U3RNP	Joint involvement	89
	Diffuse scleroderma	64
	Digital ulcers	58
	Tendon rubs	42
	Severe gastrointestinal involvement	25
	Severe pulmonary fibrosis*	24
	Isolated pulmonary hypertension*	24
	Calcinosis	22
Severe cardiac disease	18	
Muscle inflammation	18	
Th/To	Joint involvement	60
	Isolated pulmonary hypertension*	32
	Calcinosis	22
	Severe pulmonary fibrosis*	16
	Severe gastrointestinal involvement	13
Anti-Pm/Scl	Joint involvement	75
	Calcinosis	39
	Muscle inflammation	58
	Severe pulmonary fibrosis*	27
	Acroosteolysis	32

\*Pulmonary association.

hypertension had a mean DLCO of 81% predicted ( $P < .0001$ ).

### Autoantibodies

Although autoantibodies are not thought to play a role in the pathogenesis of scleroderma, they have been shown to be useful in predicting disease manifestations.<sup>9</sup> At least 7

autoantibodies are known to be associated with scleroderma phenotypes. **Table 2** lists their major clinical associations.

The highest frequency of isolated pulmonary hypertension is seen in patients with anticentromere antibodies. The presence of the nucleolar pattern on the antinuclear antibody immunofluorescence is strongly associated with the development of SScPH and usually suggests the presence of anti-Th/To, anti-U3RNP, or anti-Pm/Scl antibodies. In this group of patients, interstitial lung disease develops early in the disease course; patients are stable for several years before developing severe and often fatal pulmonary hypertension. The PH in this group is probably secondary to vasculopathy since the mean forced vital capacity (FVC) is preserved, and patients do not have sufficient hypoxia or fibrosis to account for the elevation in pulmonary artery pressure.

The 2 antibodies most commonly associated with diffuse scleroderma are the antitopoisomerase antibody (Scl-70) and the anti-RNA polymerase III antibody (Pol-3). Interstitial lung disease is seen in 25% of patients with Scl-70 antibody, but patients with this antibody have a low risk of developing PH.<sup>4</sup> In contrast, patients with Pol-3 have a striking absence of severe interstitial lung disease, similar to that seen in patients with anticentromere positive limited scleroderma.

### Clinical Presentation

In patients with IPAH one of the earliest clinical symptoms of developing PH is dyspnea on exertion. However, in scleroderma, exercise limitation due to the development of contractures and lower extremity ulcers leads to progressive adaptation to reduced exercise tolerance. As a result, dyspnea is often unrecognized, and it is not uncommon for patients with SScPH to present with acute right heart failure, pronunciation of the pulmonary component of the second heart sound, parasternal heave, elevated jugular venous pressure, and peripheral edema.

### Diagnosis and Screening

As with IPAH, the gold-standard diagnostic test for SScPH is right heart catheterization. Now that newer therapies are being developed for SScPH there is a need for a noninvasive screening test to identify patients at high risk for SScPH, so

that the disease may be identified before the vasculopathy becomes irreversible.

As discussed earlier, one of the features that has been shown to identify patients with higher risk for developing PH is the isolated reduction in DLCO and an FVC/DLCO ratio less than 1.6.<sup>4,10</sup> Regular pulmonary function testing with DLCO is recommended every 12 months for patients with scleroderma.<sup>11</sup>

Several studies have shown that asymptomatic pulmonary hypertension by echocardiographic criteria in patients with scleroderma is underrecognized. This finding has led to the recommendation for regular echocardiographic screening for at-risk scleroderma patients.<sup>3,6</sup> The implication of identifying echocardiographic evidence of PH in patients with scleroderma is not known at this time, but 2 studies have shown that not all patients meeting echocardiographic criteria for SScPH develop progressive disease. Chang and colleagues<sup>10</sup> evaluated a cohort of 457 patients with scleroderma who were being followed at John Hopkins Hospital. Study participants underwent serial echocardiograms over a mean follow-up period of 3.2 years. Findings of the study indicate that, of the 361 patients without initial evidence of PH, 25.5% went on to develop mild to moderate PH, and 13.6% progressed to severe PH. Of the patients with mild to moderate PH at baseline, 17.7% progressed to severe PH as measured by serial echocardiograms, and 15.6% regressed to having no evidence of PH. Finally, in the group with severe PH at baseline, 25% regressed to mild to moderate PH, while 3% regressed to having no evidence of PH. MacGregor and colleagues<sup>6</sup> followed scleroderma patients with elevation of pulmonary artery systolic pressure as measured by echocardiogram (> 35 mmHg) and found that, although 20% of patients died during the 3-year follow-up, 65% did not have any deterioration at 3 years.<sup>6</sup> To date, it has not been possible to identify features that predict those patients at risk of death from SScPH.

The presence of exercise-induced elevation of the pulmonary artery pressure is included in the catheterization criteria for PH. Based on studies of familial pulmonary arterial hypertension, exercise-induced PH measured by echocardiogram has been proposed as a preclinical predictor of PH.<sup>12</sup> Using an exercise echocardiogram protocol in a population of patients with scleroderma at risk for PH but with normal resting pulmonary artery systolic pressure, we identified 47% with exercise induced elevation of pulmonary artery systolic pressure (> 20 mmHg above resting pulmonary artery systolic pressure) as measured by exercise echocardiogram.<sup>13</sup> Generally, this finding correlates well with the presence of exercise-induced PH at catheterization. However, a small number of patients had false-positive exercise echocardiogram studies, and these patients had evidence of diastolic dysfunction at catheterization, substantiating the importance of right heart catheterization to confirm a diagnosis of PH.

Other researchers have shown that patients with SScPH have abnormal cardiopulmonary exercise tests compared with scleroderma patients without PH, which provides further support for exercise testing and cardiopulmonary evaluation as non-invasive screening tests for PH in patients with scleroderma.<sup>14</sup>

The implications of preclinical detection of PH remain unclear. It is not known whether intervention at a clinically asymptomatic stage can prevent development or delay progression of SScPH. A longitudinal follow-up study is ongoing, and, as with other diseases, it is hoped that earlier diagnosis and treatment may result in better outcomes.

### Biomarkers

The most promising potential biomarker for SScPH is the N-terminal pro-BNP (NT-proBNP), which has been shown to be a marker of disease severity in IPAH and is independently associated with mortality.<sup>15</sup> High NT-proBNP levels have been shown to identify SScPH with a sensitivity and specificity of 90%, positive predictive value of 69%, and negative predictive value of 96%.<sup>16</sup> In a prospective cohort of 101 patients with scleroderma without evidence of PAH at baseline, an NT-proBNP greater than 97% of normal was a predictor of developing SScPH during the 36-month follow-up ( $P = .005$ ). Use of the NT-proBNP in conjunction with a diffusion capacity to alveolar volume (DLCO/Va) ratio less than 70% was highly predictive of the development of PH during follow-up (hazard ratio 47.20, 95% confidence interval 4.9-450.33).<sup>17</sup> Finally, NT-proBNP has been shown to correlate with severity of SScPH ( $P = .02$ ), and serial changes in NT-proBNP during therapy are highly predictive of survival.<sup>18</sup>

### Pathogenesis

The pathogenesis of SScPH is unknown. The vasculopathy in SScPH is very similar to that of IPAH, with autopsy specimens that show microvascular luminal obliteration with medial and adventitial fibrosis, proliferation, and intimal hyperplasia. Altered expression of the transforming growth factor signaling pathway has been implicated, and endothelial cell activation is reported, in early SScPH.<sup>19-21</sup> Certainly, vasospasm is not thought to be the major factor in established SScPH. The response to vasodilator agents generally occurs over days or weeks, which suggests that structural remodeling rather than vasodilatation is the mechanism for the response. Profibrotic pathways probably play a role in SScPH. Endothelin receptor blockade is antifibrotic, and iloprost, the synthetic analogue of prostacyclin (PGI<sub>2</sub>), down regulates connective tissue growth factor, a downstream profibrotic mediator, which lends support to the role of fibrotic mechanisms in the development of SScPH.<sup>22,23</sup>

### Treatment

There are currently no consensus guidelines for treatment of SScPH. Only small numbers of patients with SScPH have been included in PH clinical trials because associated comorbidities such as diastolic dysfunction, interstitial lung disease, and renal disease frequently preclude their inclusion.

The American College of Chest Physicians recently revised their clinical practice guidelines for PH.<sup>24</sup> In the absence of dedicated guidelines for managing scleroderma, most experts extrapolate the treatment recommendations for idiopathic PH to the scleroderma population. We review the available data that support the use of each modality specifically with regard to that population (**Table 3**).

**Table 3. Available Therapies for SScPH**

Therapy	Drug
Supplemental oxygen	
Calcium channel blockers	
Anticoagulation	
Endothelin antagonists	Bosentan (nonselective ET inhibitor) Sitaxsentan (selective ETA inhibitor) Ambrisentan (selective ETA inhibitor)
Prostacyclin analogues	Epoprostenol Treprostinil Iloprost
Phosphodiesterase 5 inhibitors	Sildenafil

**Supplemental oxygen.** Supplemental oxygen is well-recognized as a treatment for the hypoxic vasoconstriction seen in chronic hypoxic lung disease from a variety of causes. Morgan and colleagues<sup>25</sup> studied the acute vasodilator response to oxygen in 8 patients with SScPH and 7 patients with primary PH. They found that in patients with scleroderma high-flow-oxygen therapy significantly lowered the elevated pulmonary vascular resistance from 797.6+/-179.2 to 610+/-151.6 dynes/s/cm<sup>2</sup> ( $P < .01$ ). This decrease correlated with baseline PAP ( $r = 0.86$ ,  $P < .025$ ) and PaO<sub>2</sub> ( $r = 0.77$ ,  $P < .05$ ) before oxygen therapy, which suggests that long-term domiciliary oxygen therapy may be beneficial in the treatment of hypoxic patients with SScPH.

**Calcium channel blockers.** In some patients with vasoreponsive PAH, calcium channel blockers have been shown to cause a sustained reduction in pulmonary vascular resistance and increased cardiac output. However, increasingly it is felt that their role in IPAH is limited to those patients with evidence of vasoreactivity.<sup>24</sup> It is standard care to perform an acute vasoreactivity test during the catheterization, except in those patients with low cardiac output or elevated wedge pressures in whom vasoreactivity testing can precipitate congestive heart failure.<sup>26</sup> Most patients with scleroderma are already taking calcium channel blockers or are intolerant of the adverse effects. Since a positive vasoreactivity response is rarely seen in SScPH, calcium channel blockers are generally not considered helpful.

**Oral anticoagulation.** Oral anticoagulation in the form of warfarin has been shown to have a survival benefit in IPAH.<sup>27</sup> It is postulated that patients with IPAH have increased risk of thrombosis due to right ventricular failure. SScPH is associated with positive anticardiolipin antibodies and these antibodies may contribute to endothelial injury, which suggests that there may be a role for anticoagulation in SScPH.<sup>28</sup> However, patients with scleroderma may have other comorbidities, including gastric antral vascular ectasia that can lead to an increased risk of gastrointestinal bleed-

ing; therefore, treatment with an anticoagulation agent is generally considered on a case-by-case basis.

**Endothelin antagonists.** Endothelin-1 concentrations are elevated in patients with SScPH.<sup>29</sup> Endothelin is a potent vasoconstrictor that also stimulates proliferation of smooth muscle. The actions of endothelin on smooth muscle cells are mediated through 2 receptors. Endothelin-A receptors cause smooth muscle proliferation and vasoconstriction, while endothelin-B receptors are involved with clearance of endothelin-1 and vasodilation.

The nonselective endothelin receptor antagonist bosentan has been approved for the treatment of IPAH and connective tissue disease associated pulmonary arterial hypertension (CTD-PAH). In a double-blind, placebo-controlled study that evaluated 213 patients with PH and included 22% of patients with SScPH, bosentan improved exercise capacity in both patients with IPAH and those with SScPH. However, in a retrospective study that compared IPAH and SScPH patients treated with bosentan, the subset of patients with SScPH had no improvement in functional class and a worse 2-year survival, although this did not reach statistical significance.<sup>30</sup>

With a view to targeting the vasoconstrictive actions of endothelin, 2 selective endothelin-A receptor antagonists have been developed. Ambrisentan has been approved for use in PH in the United States, while sitaxsentan is available only in Europe. There are no studies specifically addressing the use of these selective endothelin-A receptor antagonists in SScPH. However, a recent post hoc analysis of 42 patients with CTD-PAH who had been treated with sitaxsentan demonstrated improved exercise capacity, quality of life, and hemodynamics, although elevated levels in liver function tests were reported in 2 patients.<sup>31</sup>

**Phosphodiesterase-5 inhibitors.** Phosphodiesterase-5 inhibitors hinder the metabolism of cyclic guanosine monophosphate, which is required to mediate the effects of nitric oxide. Inhibition of this enzyme slows the proliferation of vascular smooth muscle cells, and, in a 12-week double-blind study in which 45% of patients had SScPH, sildenafil was shown to have beneficial effects on hemodynamics, exercise capacity, and functional class.<sup>32</sup>

**Prostacyclin analogues.** Prostacyclin stimulates the production of cyclic adenosine monophosphate, which leads to smooth muscle relaxation, inhibition of smooth muscle cell growth, and inhibition of platelet aggregation. Several prostanoid formulations are available for treatment of PAH. A 3-month randomized controlled trial that evaluated the use of intravenous poprostenol in 111 patients with SScPH demonstrated improved exercise capacity, functional class, and cardiopulmonary hemodynamics.<sup>33</sup> Similarly, a study designed to evaluate the short-term and long-term effects of poprostenol showed sustained response at 2 years in the small number of patients studied, which suggests that this drug may have a role in vascular remodeling.<sup>34</sup> Continuous subcutaneous infusion of treprostinil has been studied in patients with CTD-PH, and demonstrated improvement in exercise capacity, hemodynamics, and symptoms at 3 months.<sup>35</sup> There have been no studies evaluating iloprost, an inhaled prostacyclin analogue with a longer duration of

action, in SScPH. However, iloprost has been shown to significantly improve hemodynamics, the 6-minute walk test, functional class, and quality of life in 203 patients, including 17% of patients with underlying connective tissue disease.<sup>36</sup>

**Combination therapy.** The addition of sildenafil to bosentan monotherapy in a group of 13 patients with IPAH and 12 with SScPH found that although there was improvement in functional class and the 6-minute walk distance in the patients with IPAH, similar improvement was not seen in patients with SScPH.<sup>37</sup> The lack of improvement in this study may reflect the advanced disease in this patient group, and larger studies evaluating patients earlier in the course of their disease are needed.

**Lung transplantation.** Lung transplantation has been used in small numbers of patients with severe pulmonary dysfunction from scleroderma, but there remain only limited data on the outcomes of transplantation in SScPH. The medical records of all patients undergoing lung transplantation at 2 major centers in the United States were evaluated in a retrospective study. The findings indicate that patients with scleroderma (38% of whom had SScPH) had a small increase in early mortality at 6 months compared with patients who were undergoing transplant for IPAH and idiopathic pulmonary fibrosis. However, the results of a follow-up at 2 years showed that there was convergence in the survival rates: the 2-year cumulative survival for all patients was comparable.<sup>38</sup> Therefore, this study supports the use of lung transplantation as a viable therapeutic option for patients with advanced lung disease from scleroderma.

## Conclusion

The prevalence of SScPH is between 13% and 30% in patients with scleroderma with high associated mortality. With the advent of new therapies for SScPH, including endothelin antagonists, phosphodiesterase-5 antagonists, and prostacyclin analogues, it is hoped that the prognosis for this condition will continue to improve. Longitudinal studies are ongoing to identify an effective screening test for SScPH, so that therapy can be started before the disease becomes irreversible. ■

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