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.[1] 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.[2] 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).[3] 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.[4] 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 walk test) than patients with IPAH.[5,6] With the introduction of newer therapies for PH, the prognosis for SScPH has improved compared with historical controls.[7] Mukerjee and colleagues[2] 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.

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.

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.[8] 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.[4] 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

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Table 2. Organ Involvement in Patients With Scleroderma Specific Autoantibodies[9]

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.[9] 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.[4] 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.[4,10] Regular pulmonary function testing with DLCO is recommended every 12 months for patients with scleroderma.[11]

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.[3,6] 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[10] 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[6] 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.[6] 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.[12] 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.[13] 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 noninvasive screening tests for PH in patients with scleroderma.[14]

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.[15] 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%.[16] 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).[17] 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.[18]

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.[19-21] 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_2), down regulates connective tissue growth factor, a downstream profibrotic mediator, which lends support to the role of fibrotic mechanisms in the development of SScPH.[22,23]

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, intersitital lung disease, and renal disease frequently preclude their inclusion.

The American College of Chest Physicians recently revised their clinical practice guidelines for PH.[24] 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[25] 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^2 ($P < .01$). This decrease correlated with baseline PAP (r = 0.86, $P < .025$) and PaO_2 (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 vasoresponsive 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.[24] 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.[26] 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.[27] 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.[28] However, patients with scleroderma may have other comorbidities, including gastric antral vascular ectasia that can lead to an increased risk of gastrointestinal bleeding; 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.[29] 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.[30]

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.[31]

Phosphodiesterase-5 inhibitors. Phosphodiesterase-5 inihibitors 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.[32]

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 epoprostenol in 111 patients with SScPH demonstrated improved exercise capacity, functional class, and cardiopulmonary hemodynamics.[33] Similarly, a study designed to evaluate the short-term and long-term effects of epoprostenol 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.[34] 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.[35] 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.[36]

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.[37] 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.[38] 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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