Scleroderma and Pulmonary Hypertension(*)

Esclerodermia e Hipertensão Pulmonar

Karen A. Fagan, MD(1), David H. Collier, MD(2) e David B. Badesch, MD(3)

ABSTRACT
Patients with scleroderma are at increased risk for the development of pulmonary hypertension, and the development of unexplained dyspnea or an isolated decrease in diffusing capacity should prompt evaluation. Echocardiography is often helpful in this situation, with further testing being performed as indicated. Because the prognosis of untreated pulmonary hypertension occurring in the setting of scleroderma is generally quite poor, vigilance is required on the part of physicians following this “at risk” group of patients. The past decade has seen important advances in the treatment of pulmonary arterial hypertension, including intravenous epoprostenol, oral bosentan and subcutaneously infused treprostinil. As new therapies are developed for the treatment of pulmonary arterial hypertension, it is essential that patients with scleroderma-related disease are included in clinical trials.

Keywords: scleroderma, pulmonary hypertension, dyspnea.

RESUMO
Pacientes com esclerodermia têm risco aumentado para desenvolver hipertensão pulmonar. O aparecimento de dispnéia e/ou a diminuição da capacidade de difusão devem levar à suspeita imediata dessa complicação. A ecodopplercardiografia é importante para o diagnóstico e o seguimento desses casos. Os casos não tratados de hipertensão pulmonar em esclerodermia têm mau prognóstico, daí a necessidade em manter sob vigilância estes pacientes. Na última década surgiram avanços para o tratamento da hipertensão arterial pulmonar, incluindo os medicamentos epoprostenol EV, bosentan VO e treprostinil SC. À medida que novas terapias vão sendo desenvolvidas, torna-se necessário a realização de estudos clínicos de maior validade.

Palavras-chave: esclerodermia, hipertensão pulmonar, dispnéia.

INTRODUCTION
Pulmonary arterial hypertension is a life-threatening complication of several connective tissue diseases including scleroderma (both limited and diffuse), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD) and less commonly rheumatoid arthritis (RA) and dermatomyositis/polymyositis (Table 1). This review will discuss the clinical presentation and treatment options for patients with pulmonary hypertension and the scleroderma spectrum of diseases.

TABLE 1
CONNECTIVE TISSUE DISEASES ASSOCIATED WITH PULMONARY ARTERIAL HYPERTENSION

<table>
<thead>
<tr>
<th>Scleroderma</th>
<th>Diffuse</th>
<th>Limited</th>
<th>CREST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Mixed connective tissue disease</td>
<td>Rheumatoid arthritis</td>
<td>Dermatomyositis/polymyositis</td>
</tr>
</tbody>
</table>

* Pulmonary Hypertension Center. Division of Pulmonary Sciences and Critical Care Medicine. University of Colorado Health Sciences Center. Recebido em 29/08/03. Aprovado, após revisão, em 20/10/03.
1. Assistant Professor of Medicine. Division of Pulmonary Sciences and Critical Care Medicine, Pulmonary Hypertension Center, University of Colorado Health Sciences Center.
2. Associate Professor of Medicine. Division of Rheumatology, University of Colorado Health Sciences Center.
3. Professor of Medicine. Clinical Director, Division of Pulmonary Sciences and Critical Care Medicine, Pulmonary Hypertension Center, University of Colorado Health Sciences Center.

Correspondendo a: David B. Badesch, Clinical Director, Pulmonary Hypertension Center. Division of Pulmonary Sciences and Critical Care Medicine. University of Colorado Health Sciences Center. Box C-272 4200 E. Ninth Ave. Denver-CO 80111, USA; e-mail: david.badesch@uchsc.edu
Pulmonary hypertension may complicate several of the connective tissue diseases (Table 1). Scleroderma is a progressive, multisystemic disease manifested by connective tissue and vascular lesions in many organs, including lung, kidney and skin(1-6). Pulmonary manifestations include interstitial fibrosis, pulmonary arterial hypertension, constriction of the chest wall due to skin thickening, diaphragmatic dysfunction and chronic aspiration due to esophageal dysmotility(7). Pulmonary complications are the most frequent cause of death in patients with scleroderma(7,8), and pulmonary vascular disease has a particularly adverse effect on the prognosis(9).

The incidence of pulmonary hypertension varies between 6%-60% of patients with scleroderma(10,11). Up to 33% of patients with diffuse scleroderma have pulmonary hypertension, both isolated and in association with interstitial lung disease(10,12-16). In patients with limited scleroderma, formerly referred to as CREST (calcinosis cutis, Raynaud’s phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias), up to 60% of the patients have pulmonary hypertension(11,12,14,15,17). While not all patients have clinically significant pulmonary hypertension, two thirds of the patients with scleroderma will have pathologic evidence of pulmonary vascular disease(17,18). Stupai reported 2-year survival in patients with CREST without pulmonary hypertension to be greater than 80%, while patients with pulmonary hypertension had a 2-year survival of 40%(11). Sacks reported an overall survival of patients with pulmonary hypertension and either diffuse or limited scleroderma of approximately 50% during a 2-year observational period following diagnosis(13). Koh reported 40% survival at 2 years in patients with scleroderma and pulmonary hypertension, compared to better survival in scleroderma patients without organ failure or with other lung involvement (i.e. interstitial lung disease)(9).

Pulmonary hypertension has been reported in 4%-14% of the patients with systemic lupus erythematosus (SLE) with an overall mortality rate of 25%-50% at two years from diagnosis of pulmonary hypertension(19-25). Patients with mixed connective tissue disease (MCTD) have features of several connective tissue diseases including SLE, scleroderma, rheumatoid arthritis and polymyositis(26,27). Most MCTD patients are either predominantly SLE or scleroderma with a myositis overlap. The behavior of the disease therefore follows either a predominantly SLE or scleroderma pattern. The incidence of pulmonary hypertension in patients with MCTD is not certain but one report found two thirds of patients with MCTD had evidence of pulmonary hypertension(28) and pulmonary hypertension has been frequently cited cause of death in patients with MCTD(28-31). This high incidence of pulmonary hypertension in MCTD is probably due to the predominant scleroderma pattern of this disease in many patients with MCTD.

Rheumatoid arthritis (RA) affects 5% of the population over 65 years old and pulmonary complications include interstitial pulmonary fibrosis, rheumatoid nodules and pleural effusions. The incidence of isolated pulmonary hypertension is unknown. In a recent report, 21% of the patients with RA without evidence of other pulmonary or cardiac disease had mild pulmonary hypertension(32). The prognosis is not known. Other connective tissue diseases including dermatomyositis/polymyositis have been associated with pulmonary arterial hypertension but the incidence and prognosis are not known(33).

The etiology of pulmonary hypertension in the scleroderma spectrum of diseases remains unknown. There appears to be direct involvement of the pulmonary circulation with intimal proliferation and medial hypertrophy, somewhat similar to that seen in primary pulmonary hypertension(11,15,17,18,34,35). Some cases may also be related to severe pulmonary parenchymal disease such as interstitial disease with hypoxemia. Additionally, diastolic dysfunction of the right and left ventricles has been seen in patients with scleroderma and may lead to pulmonary hypertension(36-38).

Autoimmune processes have been implicated in the pathogenesis of pulmonary hypertension although the mechanism is not known. Positive anti-nuclear antibodies (ANA) are frequently found in pulmonary hypertension patients without a diagnosis of connective tissue disease, and pulmonary hypertension can occur before the onset of an identifiable connective tissue disease(39). In patients with scleroderma, anti-centromere and anti-histone antibodies have been associated with vascular disease(40). Anti-centromere antibodies are primarily seen in the limited form of systemic sclerosis. Since patients with the limited form of systemic sclerosis have a higher incidence of pulmonary hypertension than patients with diffuse disease, it is not surprising that anti-centromere antibodies are associated with a higher incidence of pulmonary
hypertension. Anti-fibrillarin antibodies (anti-U3-RNP) are frequently found in patients with scleroderma and are more common with diffuse scleroderma associated pulmonary hypertension\(^{(41)}\). Antiendothelial antibodies (aECA) are present in 40% and 13% of the patients with diffuse scleroderma and CREST respectively and are associated with a higher incidence of pulmonary hypertension and digital infarcts\(^{(42)}\). Anti-fibrillarin antibodies and aECAs are also associated with pulmonary hypertension in SLE\(^{(43,44)}\). In patients with scleroderma and pulmonary hypertension, especially when accompanied by HLA-B35 antigen, anti-topoisomerase II-alpha antibodies are more common as are antibodies to fibrin bound tissue type plasminogen activator (tPA)\(^{(45-47)}\).

Raynaud’s phenomenon, vasospasm of the arterioles in the distal systemic circulation, is commonly reported in patients with scleroderma. In one report, all patients with pulmonary hypertension and CREST had Raynaud’s, while 68% without pulmonary hypertension had this clinical manifestation\(^{(11)}\). Raynaud’s is also common in patients with SLE and MCTD and pulmonary hypertension\(^{(21,43,49)}\), but only 10%-14% of the patients with primary pulmonary hypertension have Raynaud’s phenomenon\(^{(49)}\). This observation has led to the “pulmonary Raynaud’s” hypothesis that vasospasm contributes to the development of pulmonary hypertension\(^{(50,51)}\). Acute hypoxic pulmonary vasoconstriction may be more pronounced in patients with pulmonary hypertension and scleroderma than in patients with primary pulmonary hypertension\(^{(52)}\). However, another report found that pulmonary vasospasm was not present in patients with Raynaud’s and scleroderma without pulmonary hypertension\(^{(53)}\). Supporting this hypothesis, endothelial dysfunction may be important in the development of pulmonary hypertension\(^{(54,55)}\). Patients with scleroderma have defective endothelial-dependent vasodilatation\(^{(29)}\) and this may be related to decreased nitric oxide synthase (eNOS)\(^{(56)}\). Decreased lung eNOS has been reported in severe primary pulmonary hypertension\(^{(57,58)}\). While the level of eNOS in connective tissue disease is not known, decreased production of lung NO has been found in patients with scleroderma and pulmonary hypertension\(^{(59,60)}\). Similarly, the expression of prostacyclin synthase in pulmonary endothelium may be decreased in patients with severe connective tissue disease associated with pulmonary hypertension\(^{(61)}\).

Endothelin-1 is increased in serum of patients with both diffuse and limited scleroderma\(^{(62,63)}\), and while endothelin levels correlate with survival in patients with scleroderma\(^{(64)}\), they were not higher in those patients with pulmonary hypertension\(^{(62)}\). In contrast, higher serum endothelin levels are found in patients with SLE associated pulmonary hypertension than non-pulmonary hypertensive SLE patients\(^{(23)}\). The potential role of ET-1 in pulmonary hypertension has led to the use of endothelin antagonists in the treatment of patients with connective tissue disease associated pulmonary hypertension\(^{(65,66)}\). Serotonin may also play a role in the pathogenesis of pulmonary hypertension. In patients with systemic sclerosis and Raynaud’s phenomenon, platelet serotonin concentrations are decreased and serum levels are increased\(^{(67,68)}\).

**CLINICAL PRESENTATION AND EVALUATION**

Dyspnea is the most common symptom of scleroderma presenting pulmonary hypertension. The clinical evaluation is similar to that of patients with primary pulmonary hypertension. History and physical examination often reveal findings of the underlying connective tissue disease (i.e. Raynaud’s phenomenon, telangiectasias, rash, synovitis, interstitial lung disease, etc.). Decreased diffusing capacity of the lung is the most common pulmonary function abnormality and should prompt an evaluation for both pulmonary vascular and interstitial lung disease\(^{(69)}\). A diffusing capacity lower than 40% of that predicted for lung volume places the patient in a poor prognostic category. Echocardiography may be helpful in the evaluation of patients suspected of having pulmonary hypertension as suggested by unexplained dyspnea or an isolated reduction in diffusing capacity. As previously discussed, patients with scleroderma should be considered an “at risk” group for the development of pulmonary hypertension, and echocardiography may reveal right ventricular hypertrophy and dilatation even before the onset of symptoms\(^{(70,71)}\). Ultimately, as with primary pulmonary hypertension, right heart catheterization is needed to confirm the diagnosis, assess hemodynamic severity and exclude other possible contributing factors such as an occult congenital heart defect. While it is generally thought that patients with scleroderma associated pulmonary hypertension are less likely to demonstrate a favorable response to vasodilator therapy than patients with primary pulmonary hypertension (in whom the response rate is approximately 20%-25%), a hemodynamically monitored assessment of vasoreactivity is still advocated by some experts.
Several therapeutic options are available for the treatment of scleroderma-associated pulmonary hypertension (Table 2). Oral vasodilators (calcium channel antagonists, angiotensin converting enzyme inhibitors, and alpha-adrenergic antagonists) have been used to treat pulmonary hypertension in patients with scleroderma. Although it has been reported that calcium channel blockers have improved survival in some patients with scleroderma-associated pulmonary hypertension, it is generally acknowledged that only a small percentage of such patients respond favorably to these agents. Angiotensin converting enzyme inhibitors and alpha-adrenergic blockers (prazosin) have also been used both acutely and in the long term on the treatment of connective tissue disease-associated pulmonary hypertension.

**Table 2**

**Potential Therapeutic Options for Scleroderma Pulmonary Hypertension**

<table>
<thead>
<tr>
<th>Vasodilators</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td></td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td></td>
</tr>
<tr>
<td>Alpha-adrenergic blockers</td>
<td></td>
</tr>
<tr>
<td>Prostaglandin preparations</td>
<td></td>
</tr>
<tr>
<td>IV epoprostenol</td>
<td></td>
</tr>
<tr>
<td>SC treprostinil</td>
<td></td>
</tr>
<tr>
<td>Inhaled iloprost</td>
<td></td>
</tr>
<tr>
<td>Inhaled Nitric Oxide</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endothelin antagonists</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serotonin antagonists</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketanserin</td>
<td></td>
</tr>
<tr>
<td>Sarpogrelate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunosuppressive therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung/Heart Lung transplantation</th>
<th></th>
</tr>
</thead>
</table>

In a randomized, multicentric study of continuously intravenously infused epoprostenol, improvement was seen in patients with pulmonary hypertension due to scleroderma. 111 patients with pulmonary hypertension and the scleroderma spectrum of disease (70% with limited disease, 13% with diffuse disease, 11%–14% with overlap syndrome, and 5% with features of scleroderma) were randomized to receive continuous infusion of epoprostenol vs. conventional treatment for 12 weeks. Epoprostenol improved exercise capacity, cardiopulmonary hemodynamics, New York Heart Association functional class, Borg dyspnea scale and likely Raynaud’s phenomenon. However, there was no mortality benefit as has been seen in the same treatment duration with primary pulmonary hypertension, possibly due to the multisystemic nature of this disease. It is important to point out that the study was not powered to detect a survival difference. Others have also found both short and long-term improvement with epoprostenol. Long-term follow-up of the patients in our study has suggested that epoprostenol may improve survival compared to historical controls. However, in general it appears as though survival/prognosis is worse for scleroderma-associated pulmonary hypertension as compared to patients with primary pulmonary hypertension. Treatment with epoprostenol in some patients has been associated with reports of pulmonary edema possibly due to the presence of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis. As it is very rare, pulmonary veno-occlusive disease may be more common in patients with connective tissue disease.

Increasing evidence has suggested the importance of endothelin-1 in the pathogenesis of pulmonary hypertension. In a multicentric, randomized, double-blinded placebo controlled trial of endothelin receptor blocker bosentan (Tracleer®) for the treatment of pulmonary arterial hypertension, 213 patients with pulmonary hypertension, either primary or due to connective tissue disease (scleroderma and lupus), were randomized to receive placebo or bosentan at 125 mg or 250 mg orally twice daily. After 16 weeks, distance walked in six minutes, functional class, Borg dyspnea index and time to clinical worsening improved in patients receiving bosentan. In contrast to the improvement in patients with primary pulmonary hypertension, bosentan prevented the deterioration in six-minute walking compared to placebo, suggesting that patients with scleroderma did less well overall. Nevertheless, relative stability may represent a favorable outcome in a disease with an otherwise very poor prognosis. Bosentan has been associated with a dose-dependent incidence of increased liver function tests, and monthly follow-up of these tests is required by the United States Food and Drug Administration.
Administration. Other potential side effects are thought to include mild anemia, fluid retention, teratogenicity, and possibly testicular dysfunction and male infertility. Even in the light of these potential adverse effects, the development of this oral therapy is thought to represent a significant advance.

Various prostacyclin analogues and delivery systems have been studied recently. Inhaled iloprost, a stable analogue of epoprostenol, was tested in 5 patients with limited CREST and severe pulmonary hypertension. After one year, quality of life, functional class and hemodynamics improved, and this improvement was maintained for 2 years in 3 of 5 patients\(^86\). Treprostinil, a stable prostacyclin analogue administered subcutaneously, was approved for use in patients with pulmonary arterial hypertension\(^88\). Beraprost sodium, an orally bioactive prostacyclin analogue, improved six-minute walking distance in patients with primary pulmonary hypertension but not in patients with connective tissue disease\(^86\).

Although NO has utility in acute pulmonary vasodilator testing in patients with scleroderma, there have not been any reports of long-term use of NO in the treatment of scleroderma associated pulmonary hypertension\(^87\). The selective serotonin receptor 2 antagonist ketanserin acutely improved pulmonary artery pressure and cardiac output in patients with scleroderma associated pulmonary hypertension\(^88\), while sarpogrelate, another serotonin receptor 2 antagonist, administered orally for 12 months, decreased mean pulmonary arterial pressure and increased right ventricular ejection fraction\(^89\). These reports suggest a role for serotonin in the pathogenesis of scleroderma associated pulmonary arterial hypertension although a randomized, controlled trial has not been done.

Corticosteroids with and without cyclophosphamide\(^25\), long-term plasma exchange\(^86\) and autologous stem cell transplantation\(^91\) have been reported to improve or stabilize pulmonary hypertension in patients with scleroderma. However, these represent case reports or retrospective case studies and no prospective study of immunosuppressive therapy has been completed in patients with connective tissue disease related to pulmonary hypertension. Using immunosuppressive therapy may be more successful in patients with SLE than scleroderma.

Surgical treatment, including atrial septostomy\(^92\) and lung or heart-lung transplantation, may be considered for patients with severe pulmonary arterial hypertension in association with connective tissue disease. Survival in patients with connective tissue disease associated pulmonary hypertension who undergo lung or heart-lung transplantation was not different than in patients with primary pulmonary hypertension\(^93\). Lung transplant may also be beneficial to patients with severe fibrotic lung disease. Appropriate patient selection is important, though, and lung transplantation may be relatively contraindicated in patients with significant esophageal dysmotility or renal dysfunction.

---

REFERENCES


