Scleroderma-Associated Pulmonary Hypertension: Who's at Risk and Why

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Introduction

Pulmonary arterial hypertension is a life-threatening complication of several connective tissue diseases, including both diffuse and limited scleroderma (with a subgroup of limited scleroderma called the CREST syndrome), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and less commonly, rheumatoid arthritis, and dermatomyositis/polymyositis (**Table 1**). This review will discuss the incidence, potential etiologies, 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

Scleroderma
Diffuse
Limited
CREST
Systemic lupus erythematosis
Mixed connective tissue disease
Rheumatoid arthritis
Dermatomyositis/Polymyositis

Epidemiology

Pulmonary hypertension complicates several of the connective tissue diseases (**Table 1**). Scleroderma is a progressive, multisystem disease manifested by connective tissue and vascular lesions in many organs, including lung, kidney, and skin. 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.[1] Pulmonary complications are the most frequent cause of death in patients with scleroderma,[1] and pulmonary vascular disease has a particularly adverse effect on prognosis.[2]

The incidence of pulmonary hypertension varies between 6% and 60% of patients with scleroderma. Up to 33% of patients with diffuse scleroderma have pulmonary hypertension, both isolated and in association with interstitial lung disease.[3-6] In patients with limited scleroderma, formerly referred to as CREST (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias), up to 60% of patients have pulmonary hypertension.[4, 6-8] While not all patients have clinically significant pulmonary hypertension, two thirds of patients with scleroderma will have pathologic evidence of pulmonary vascular disease.[7, 9] Stupi et al reported two-year survival in patients with CREST without pulmonary hypertension to be greater than 80% while patients with pulmonary hypertension had a two-year survival of 40%.[8] Sacks et al reported two-year survival of patients with pulmonary hypertension and either diffuse or limited scleroderma to be approximately 50%.[5] Koh et al reported 40% survival in patients with scleroderma and pulmonary hypertension compared with higher survival in scleroderma patients without organ failure or with other lung involvement (i.e. interstitial lung disease) at two years.[2]

Pulmonary hypertension has been reported in 4% to 14% of patients with systemic SLE with an overall mortality rate of 25% to 50% at two years from diagnosis of pulmonary hypertension.[10-13] Patients with MCTD have features of several connective tissue diseases, including SLE, scleroderma, rheumatoid arthritis, and polymyositis. Most MCTD patients have either predominantly SLE or scleroderma with a myositis overlap. The behavior of the disease therefore follows either a predominantly SLE or a 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[14] and pulmonary hypertension has been frequently cited as a cause of death in patients with MCTD.[15] The high incidence of pulmonary hypertension in MCTD is probably a result of the predominant scleroderma pattern of this disease in many patients with MCTD.

Rheumatoid arthritis affects 5% of the population over age 65 and pulmonary complications include interstitial pulmonary fibrosis, rheumatoid nodules, and pleural effusions. The incidence of isolated pulmonary hypertension is not known. In a recent report, 21% of patients with rheumatoid arthritis without evidence of other pulmonary or cardiac dis-

ease had mild pulmonary hypertension.[16] 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.[17]

Pathogenesis

The etiology of pulmonary hypertension in the scleroderma spectrum of diseases remains obscure. There appears to be direct involvement of the pulmonary circulation with intimal proliferation and medial hypertrophy, similar to that seen in primary pulmonary hypertension.[6-9, 18] 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 contribute to pulmonary hypertension.[19]

Autoimmune processes have been implicated in the pathogenesis of pulmonary hypertension although the mechanism is not known. Positive antinuclear antibodies 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. In patients with scleroderma, anticentromere and antihistone antibodies have been associated with vascular disease. Anticentromere 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 do patients with diffuse disease, it is not surprising that anticentromere antibodies would be associated with a higher incidence of pulmonary hypertension. Antifibrillarin antibodies (anti-U3-RNP) are frequently found in patients with scleroderma and are more common with diffuse scleroderma-associated pulmonary hypertension.[20] Antiendothelial antibodies (aECA) are present in 40% and 13% of patients with diffuse scleroderma and CREST, respectively, and are associated with a higher incidence of pulmonary hypertension and digital infarcts.[21] Antifibrillarin antibodies and aECAs are also associated with pulmonary hypertension in SLE.[22] In patients with scleroderma and pulmonary hypertension, especially when accompanied by HLA-B35 antigen, antitopoisomerase II-alpha antibodies are more common, as are antibodies to fibrin-bound tissue type plasminogen activator.[23]

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 Raynaud's.[8] Raynaud's is also common in patients with SLE and MCTD and pulmonary hypertension[11, 24] but only 10% to 14% of patients with primary pulmonary hypertension have Raynaud's.[25] This observation has led to the "pulmonary Raynaud's" hypothesis that vasospasm contributes to the development of pulmonary hypertension.[26]

Acute hypoxic pulmonary vasoconstriction may be more pronounced in patients with pulmonary hypertension and scleroderma than in patients with primary pulmonary hypertension.[27] However, another report found that pulmonary vasospasm was not present in patients with Raynaud's and scleroderma without pulmonary hypertension.[28] In support of this hypothesis, patients with scleroderma have defective endothelial-dependent vasodilation[15] and this may be related to decreased endothelial nitric oxide synthase (eNOS).[29] Although controversial, decreased lung eNOS has been reported in severe primary pulmonary hypertension.[30] While the level of eNOS in connective tissue disease is not known, decreased production of lung nitric oxide has been found in patients with scleroderma and pulmonary hypertension.[31] Similarly, expression of prostacyclin synthase in pulmonary endothelium may be decreased in patients with severe connective tissue disease-associated pulmonary hypertension.[32]

Endothelin-1 is increased in serum of patients with both diffuse and limited scleroderma[33] and while endothelin levels correlate with survival in patients with scleroderma,[34] they are not higher in those with pulmonary hypertension.[33] In contrast, higher serum endothelin levels are found in patients with SLE-associated pulmonary hypertension than in nonpulmonary hypertensive SLE patients.[12] The role of endothelin-1 in pulmonary hypertension has led to the use of endothelin antagonists in treatment of patients with connective tissue disease-associated pulmonary hypertension.[35] Serotonin may also play a role in the pathogenesis of pulmonary hypertension. In patients with systemic sclerosis and Raynaud's, platelet serotonin concentrations are decreased and serum levels are increased.[36, 37]

Clinical Presentation and Evaluation

Dyspnea is the most common presenting symptom of scleroderma-associated 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 (ie, Raynaud's, 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.[38] A diffusing capacity of less than 40% of 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.[39] 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% to 25%), a hemodynamically monitored assessment of vasoreactivity is still advocated by some experts.

Table 2—Potential Therapeutic Options

- **Vasodilators**
  - Calcium channel blockers
  - Angiotensin converting enzyme inhibitors
  - Alpha-adrenergic blockers
  - Prostaglandin preparations
    - Intravenous epoprostenol
    - Subcutaneous treprostinil
    - Inhaled iloprost
    - Inhaled nitric oxide
- **Phosphodiesterase inhibitors**
- **Endothelin receptor antagonists**
- **Serotonin antagonists**
- **Immunosuppressive therapy**
  - Corticosteroids
  - Cyclophosphamide
  - Bone marrow transplantation
- **Lung/Heart-lung transplantation**

Therapy

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,[40-42] it is generally acknowledged that only a small percentage of such patients respond favorably to these agents. Angiotensin converting enzyme inhibitors and an alpha-adrenergic blocker (prazosin) have also been used both acutely and over the long term in the treatment of connective tissue disease-associated pulmonary hypertension.[41,43]

In a randomized, multicenter study of continuously intravenously infused epoprostenol we reported short-term improvement in patients with pulmonary hypertension due to scleroderma;[44] 111 patients with pulmonary hypertension and the scleroderma spectrum of disease (70% limited disease, 13% diffuse disease, 11% to 14% 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 index, and likely Raynaud's. However, there was no mortality benefit as had been seen in the same treatment duration with primary pulmonary hypertension,[45] possibly because of the multisystem nature of this disease.[44] 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.[46,47] Long-term follow up of the patients in our study has suggested that epoprostenol may improve survival compared with historical controls. However, in general it appears as though survival/prognosis is worse for patients with scleroderma-associated pulmonary hypertension as compared with patients with primary pulmonary hypertension and needs further investigation. Treatment with epoprostenol in some patients has been associated with reports of pulmonary edema possibly resulting from pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis.[48] Although very rare, pulmonary veno-occlusive disease may be more common in patients with connective tissue disease.[49]

Increasing evidence has suggested the importance of endothelin-1 in the pathogenesis of pulmonary hypertension. In a multicenter, randomized, double-blinded placebo controlled trial of the endothelin receptor antagonist 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 or 250 mg orally twice daily.[35] After 16 weeks, distance walked in six minutes, functional class, Borg dyspnea index, and time to clinical worsening improved in patients receiving either dose of bosentan. In contrast to the improvement in patients with primary pulmonary hypertension, bosentan prevented the deterioration in six-minute walk compared with placebo. This suggested 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 increase in liver function tests, and monthly follow-up of these tests is required by the Food and Drug Administration. Other potential side effects are thought to include mild anemia, fluid retention, teratogenicity, and possibly testicular dysfunction and male infertility. Even in 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 recently studied. Inhaled iloprost, a stable analogue of epoprostenol, was studied in a large placebo-controlled trial comparing inhaled iloprost with placebo in patients with severe pulmonary hypertension. Iloprost improved six-minute walk test results, functional status, and hemodynamics after 12 weeks of treatment.[50] The effect was greatest in patients with primary pulmonary hypertension. Combination with a phosphodiesterase inhibitor appears to increase the effectiveness of inhaled iloprost in patients with pulmonary hypertension.[51] Treprostinil, a stable prostacyclin analogue administered subcutaneously, was recently approved for use in patients with pulmonary arterial hypertension with efficacy at the highest doses of the drug.[52] Beraprost sodium, an orally bioactive prostacyclin analogue, improved six-minute walk distance in patients with primary pulmonary hypertension compared with patients with connective tissue disease.[53]

Although nitric oxide has utility in acute pulmonary vasodilator testing in patients with scleroderma, there have not been any reports of its long-term use in the treatment of scleroderma-associated pulmonary hypertension. The selective serotonin receptor 2 antagonist ketanserin acutely improved pulmonary artery pressure and cardiac output in patients with scleroderma-associated pulmonary hypertension[54] while sar-

pogrelate, another receptor 2 antagonist, administered orally for 12 months, decreased mean pulmonary arterial pressure and increased right ventricular ejection fraction.[55] 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,[13] long-term plasma exchange,[56] and autologous stem cell transplantation[57] 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 pulmonary hypertension. Use of immunosuppressive therapy may be more successful in patients with SLE than in those with scleroderma.

Surgical treatment, including atrial septostomy[58] 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 is not different from that in patients with primary pulmonary hypertension.[59] Lung transplantation may also be of benefit in 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.

Summary

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. 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. **PH**

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References

1. Minai OA, Dweik RA, Arroliga AC. Manifestations of scleroderma pulmonary disease. *Clin Chest Med* 1998;19(4):713-31, viii-ix.
2. Koh ET, Lee P, Gladman DD, et al. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. *Br J Rheumatol* 1996;35 (10):989-93.
3. Battle RW, Davitt MA, Cooper SM, et al. Prevalence of pulmonary hypertension in limited and diffuse scleroderma. *Chest* 1996;110 (6):1515-9.
4. MacGregor AJ, Canavan R, Knight C, et al. Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. *Rheumatology* (Oxford) 2001;40(4):453-9.
5. Sacks DG, Okano Y, Steen VD, et al. Isolated pulmonary hypertension in systemic sclerosis with diffuse cutaneous involvement: association with serum anti-U3RNP antibody. *J Rheumatol* 1996;23(4):639-42.
6. Ungerer RG, Tashkin DP, Furst D, et al. Prevalence and clinical correlates of pulmonary arterial hypertension in progressive systemic sclerosis. *Am J Med* 1983;75(1):65-74.
7. Salerni RG, Rodnan P, Leon DF, et al. Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). *Ann Intern Med* 1977;86(4):394-9.
8. Stupi AM, Steen VD, Owens GR, et al. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986;29 (4):515-24.
9. Young RH, Mark GJ. Pulmonary vascular changes in scleroderma. *Am J Med* 1978;64(6):998-1004.
10. Asherson RA, Higenbottam TW, Dinh Xuan AT, et al. Pulmonary hypertension in a lupus clinic: experience with twenty-four patients. *J Rheumatol* 1990;17(10):1292-8.
11. Li EK, Tam LS. Pulmonary hypertension in systemic lupus erythematosus: clinical association and survival in 18 patients. *J Rheumatol* 1999;26(9):1923-9.
12. Shen JY, Chen SL, Wu YX, et al. Pulmonary hypertension in systemic lupus erythematosus. *Rheumatol Int* 1999;18(4):147-51.
13. Tanaka E, Harigai M, Tanaka M, et al. Pulmonary hypertension in systemic lupus erythematosus: evaluation of clinical characteristics and response to immunosuppressive treatment. *J Rheumatol* 2002;29(2): 282-7.
14. Prakash UB. Respiratory complications in mixed connective tissue disease. *Clin Chest Med* 1998;19(4):733-46, ix.
15. Burdt MA, Hoffman RW, Deutscher SL, et al. Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. *Arthritis Rheum* 1999;42(5):899-909.
16. Dawson JK, Goodson NG, Graham DR, et al. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. *Rheumatology* (Oxford) 2000;39(12):1320-5.
17. Denbow CE, Lie JT, Tancredi RG, et al. Cardiac involvement in polymyositis: a clinicopathologic study of 20 autopsied patients. *Arthritis Rheum* 1979;22(10):1088-92.
18. Yousem SA. The pulmonary pathologic manifestations of the CREST syndrome. *Hum Pathol* 1990;21(5):467-74.
19. Giunta A, Tirri E, Maione S, et al. Right ventricular diastolic abnormalities in systemic sclerosis. Relation to left ventricular involvement and pulmonary hypertension. *Ann Rheum Dis* 2000;59(2):94-8.
20. Tormey VJ, Bunn CC, Denton CP, et al. Anti-fibrillarin antibodies in systemic sclerosis. *Rheumatology* (Oxford) 2001;40(10):1157-62.
21. Negi VS, Tripathy NK, Misra R, et al. Antiendothelial cell antibodies in scleroderma correlate with severe digital ischemia and pulmonary arterial hypertension. *J Rheumatol* 1998;25(3):462-6.
22. Yoshio T, Masuyama J, Sumiya M, et al. Antiendothelial cell antibodies and their relation to pulmonary hypertension in systemic lupus erythematosus. *J Rheumatol* 1994;21(11):2058-63.
23. Grigolo B, Mazzetti I, Meliconi R, et al. Anti-topoisomerase II alpha autoantibodies in systemic sclerosis- association with pulmonary hypertension and HLA-B35. *Clin Exp Immunol* 2000;121(3):539-43.
24. Ueda N, Mimura K, Maeda H, et al. Mixed connective tissue disease with fatal pulmonary hypertension and a review of literature. *Virchows Arch A Pathol Anat Histopathol* 1984;404(4):335-40.
25. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;107(2): 216-23.
26. Fahey PJ, Utell MJ, Condemi JJ, et al. Raynaud's phenomenon of the lung. *Am J Med* 1984;76(2):263-9.

27. Morgan JM, Griffiths M, du Bois RM, et al. Hypoxic pulmonary vasoconstriction in systemic sclerosis and primary pulmonary hypertension. *Chest* 1991;99(3):551-6.
28. Shuck JW, Oetgen WJ, Tesar JT. Pulmonary vascular response during Raynaud's phenomenon in progressive systemic sclerosis. *Am J Med* 1985;78(2):221-7.
29. Romero LI, Zhang DN, Cooke JP, et al. Differential expression of nitric oxide by dermal microvascular endothelial cells from patients with scleroderma. *Vasc Med* 2000;5(3):147-58.
30. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1995;333(4):214-21.
31. Rolla G, Colagrande P, Scappaticci E, et al. Exhaled nitric oxide in systemic sclerosis: relationships with lung involvement and pulmonary hypertension. *J Rheumatol* 2000;27(7):1693-8.
32. Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999;159(6):1925-32.
33. Morelli S, Ferri C, Polettini E, et al. Plasma endothelin-1 levels, pulmonary hypertension, and lung fibrosis in patients with systemic sclerosis. *Am J Med* 1995;99(3):255-60.
34. Galie N, Bacchi-Reggiani GF, et al. Relation of endothelin-1 to survival in patients with primary pulmonary hypertension. European Journal of Clinical Investigation 1996;26(suppl 1):48.
35. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346(12):896-903.
36. Klimiuk PS, Grennan A, Weinkove C, et al. Platelet serotonin in systemic sclerosis. *Ann Rheum Dis* 1989;48(7):586-9.
37. Biondi ML, Marasini B, Bianchi E, et al. Plasma free and intraplatelet serotonin in patients with Raynaud's phenomenon. *Int J Cardiol* 1988;19(3):335-9.
38. Scheja A, Akesson A, Wollmer P, et al. Early pulmonary disease in systemic sclerosis: a comparison between carbon monoxide transfer factor and static lung compliance. *Ann Rheum Dis* 1993;52(10):725-9.
39. Denton CP, Cailes JB, Phillips GD, et al. Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. *Br J Rheumatol* 1997;36(2):239-43.
40. Alpert MA, Pressly TA, Mukerji V, et al. Acute and long-term effects of nifedipine on pulmonary and systemic hemodynamics in patients with pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease. *Am J Cardiol* 1991;68(17):1687-91.
41. Glikson M, Pollack A, Dresner-Feigin R, et al. Nifedipine and prazosin in the management of pulmonary hypertension in CREST syndrome. *Chest* 1990;98(3):759-61.
42. Shinohara S, Murata I, Yamada H, et al. Combined effects of diltiazem and oxygen in pulmonary hypertension of mixed connective tissue disease. *J Rheumatol* 1994;21(9):1763-5.
43. Alpert MA, Pressly TA, Mukerji V, et al. Short- and long-term hemodynamic effects of captopril in patients with pulmonary hypertension and selected connective tissue disease. *Chest* 1992;102(5):1407-12.
44. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;132(6):425-34.
45. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. 1996; *N Engl J Med* 334(5):296-302.
46. Humbert M, Sanchez O, Fartoukh M, et al. Treatment of severe pulmonary hypertension secondary to connective tissue diseases with continuous IV epoprostenol (prostacyclin). *Chest* 1998;114(1 Suppl):80S-82S.
47. Klings ES, Hill NS, Ieong MH, et al. Systemic sclerosis-associated pulmonary hypertension: short- and long- term effects of epoprostenol (prostacyclin). *Arthritis Rheum* 1999;42(12):2638-45.
48. Resten A, Maitre S, Humbert M, et al. Pulmonary arterial hypertension: thin-section CT predictors of epoprostenol therapy failure. *Radiology* 2002;222(3):782-8.
49. Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. *Am J Respir Crit Care Med* 2000;162(5):1964-73.
50. Olschewski H, Simonneau G, Galie N, et al. for the Aerosolized Iloprost Randomized Study Group. Inhaled Iloprost for Severe Pulmonary Hypertension. *N Eng J Med* 2002;347(5):322-329.
51. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002;136(7):515-22.
52. Simonneau G, Barst RJ, Galie N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165(6):800-4.
53. Galie N, Humbert M, Vachiery JL, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;39(9):1496-502.
54. Seibold JR, Molony RR, Turkevich D, et al. Acute hemodynamic effects of ketanserin in pulmonary hypertension secondary to systemic sclerosis. *J Rheumatol* 1987;14(3):519-24.
55. Kato S, Kishiro I, Machida M, et al. Suppressive effect of sarpogrelate hydrochloride on respiratory failure and right ventricular failure with pulmonary hypertension in patients with systemic sclerosis. *J Int Med Res* 2000;28(6):258-68.
56. Ferri C, Emdin M, Storino FA, et al. Isolated pulmonary hypertension in diffuse cutaneous systemic sclerosis successfully treated with long-term plasma exchange. *Scand J Rheumatol* 2000;29(3):198-200.
57. Binks M, Passweg JR, Furst D, et al. Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. *Ann Rheum Dis* 2001;60(6):577-84.
58. Allcock RJ, O'Sullivan JJ, Corris PA. Palliation of systemic sclerosis-associated pulmonary hypertension by atrial septostomy. *Arthritis Rheum* 2001;44(7):1660-2.
59. Rosas VJ, Conte V, Yang SC, et al. Lung transplantation and systemic sclerosis. *Ann Transplant* 2000;5(3):38-43.