

Pulmonary Hypertension in Systemic Sclerosis

Muhammad Ishaq Ghauri¹,
Jibran Sualeh Muhammad² and Kamran Hameed³

¹Department of Medicine, Jinnah Medical College Hospital

²Department of Biological and Biomedical Sciences, Aga Khan University

³Department of Medicine, Ziauddin Medical University, Karachi,
Pakistan

1. Introduction

Pulmonary complications of systemic sclerosis (SSc) are both frequent and the leading cause of SSc-related death (Steen & Medsger, 2007; Ferri *et al.*, 2002). The most common pulmonary manifestations of SSc are the following:

- Pulmonary arterial hypertension (PAH)
- Interstitial lung disease (ILD)
- Pulmonary hypertension (PH) due to ILD
- A combination of ILD and PAH

2. Classification

The World Health Organization (WHO) classifies patients with pulmonary hypertension into five groups, as shown in the table (table 1) (Simonneau *et al.*, 2009).

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn

1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1: activin receptor-like kinase type 1; BMPR2: bone morphogenetic protein receptor type 2;
HIV: human immunodeficiency virus.

Table 1.

Patients in the first group are considered to have pulmonary arterial hypertension (PAH). In contrast, patients in the remaining four groups are considered to have pulmonary hypertension (PH):

- Group 2 PH consists of patients who have pulmonary venous hypertension, which is usually due to left heart disease
- Group 3 PH includes patients who have PH due to lung disease and/or chronic hypoxemia (ie, interstitial lung disease, chronic obstructive airways disease, and obstructive sleep apnea)
- Group 4 PH consists of patients with chronic thromboembolic pulmonary hypertension
- Group 5 PH includes patients whose PH is of uncertain cause and likely multifactorial

When all five groups are described collectively, the term PH is used.

Systemic sclerosis (SSc) is unique among the different forms of PH because it can be associated with group 1 PAH or group 3 PH. In addition, patients with SSc frequently have diastolic dysfunction and group 2 PH. As a result, the precise classification of the type of PH can be challenging in patients with SSc. Group 1 PAH is the focus of this review.

3. Definition

Systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest (measured by right heart catheterization) with a wedge pressure less than or equal to 15 mmHg in a patient who has systemic sclerosis without significant coexisting interstitial lung disease and chronic hypoxemia. (Badesch *et al.*, 2009)

4. Risk factors

It is important to recognize patients who are at increased risk for developing systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH). Vigilant monitoring and early detection facilitates the timely initiation of therapy, which improves symptoms and may prolong survival.

The following risk factors for PAH have been identified in patients with SSc:

- Long-standing limited cutaneous SSc with a positive anti-centromere antibody. The total burden of cutaneous telangiectasias correlates positively with the risk of PAH. (Shah *et al.*, 2010)
- Patients with diffuse cutaneous SSc tend to develop PAH less commonly; however, those with a nucleolar pattern of anti-nuclear antibody (ANA) are at increased risk. (Steen, 2005)
- Progressive decrease of the diffusion capacity (DLCO) over serial measurements. This was demonstrated by a case control study of 212 patients with limited cutaneous SSc (Steen & Medsger, 2003). Patients with PAH were matched to patients without PAH according to age, gender, extent of skin involvement, and disease duration. The mean DLCO was 52 percent of predicted five years before PAH developed. A linear decline of 50 percent was found over a 10 to 15 year period among patients who developed PAH. In contrast, the DLCO remained unchanged in patients who did not develop PAH.
- Exercise-induced PH on right heart catheterization. Nearly 20 percent of patients with SSc and exercise-induced PH may progress to PAH, according to an observational study. (Steen *et al.*, 2008; Condliffe *et al.*, 2009)

In contrast to these risk factors, patients with Scl 70 autoantibodies are more likely to have PH associated with interstitial lung disease (group 3 PH). Patients with SSc who have anti-RNA polymerase III autoantibodies characteristically have extensive skin involvement and increased risk for scleroderma renal crisis, but uncommonly develop PAH. (Steen, 2005)

5. Screening

Patients with systemic sclerosis (SSc) who have never been diagnosed with pulmonary vascular disease have been screened for pulmonary arterial hypertension (PAH) in numerous observational studies. Doppler echocardiography was the most common screening method, but exercise echocardiography and diagnostic algorithms were also used:

- Doppler echocardiography – In a study that included 669 patients with SSc or mixed connective tissue disease, 13 percent had an elevated right ventricular systolic pressure (an indicator of PAH). In another study of 227 patients with SSc, serial Doppler echocardiograms found a high tricuspid gradient (also an indicator of PAH) in 11

- percent of patients during the initial echocardiogram and 17 percent during a subsequent echocardiogram. (Wigley *et al.*, 2005; Hesselstrand *et al.*, 2005)
- Exercise echocardiography – A study of 54 patients with SSc found that 44 percent had an abnormal response to exercise (defined as a ≥ 20 mmHg increase of the estimated pulmonary arterial systolic pressure during exercise, as measured echocardiographically) (Steen *et al.*, 2008). Right heart catheterization confirmed the presence of resting or exercise induced PAH in 81 percent of these patients. Thus, resting PAH was identified in nearly 36 percent of the study population. Of note, the abnormal response to exercise strongly correlated with a very low diffusion capacity (DLCO) and a high forced vital capacity to DLCO ratio (FVC/DLCO).
 - Diagnostic algorithms – A study of 709 patients who had SSc identified PAH in 8 percent of the patients using an algorithm that included Doppler echocardiography and right heart catheterization. (Hachulla *et al.*, 2005)

Taken together, the studies have estimated that the prevalence of PAH is 8 to 37 percent among patients with SSc who have never been diagnosed with pulmonary vascular disease range (Steen *et al.*, 2008; Wigley *et al.*, 2005; Hesselstrand *et al.*, 2005; Hachulla *et al.*, 2005). This high prevalence, combined with the high mortality rate of SSc-associated PAH and the availability of therapies that improve symptoms and may prolong survival, has been used as an argument to screen patients who have SSc for PAH.

These factors must be weighed against the potential pitfalls of screening, which include the impact of false positive and false negative results. False positive results may lead to unnecessary right heart catheterization and related complications, as well as unnecessary patient anxiety. False negative results may lead to false reassurance and decreased vigilance in the clinical assessment of symptoms and signs of PAH, ultimately delaying diagnosis and therapy. False positive and false negative results are most common among patients who have interstitial lung disease. (Arcasoy *et al.*, 2003)

All patients with SSc should be evaluated regularly and thoroughly for symptoms and/or signs of PAH, as well as having regular pulmonary function tests (PFTs) to look for changes in the diffusion capacity (DLCO).

The diagnostic evaluation of suspected SSc-associated PAH is the same as that for other types of PAH, which is discussed in detail elsewhere. Suspected SSc-associated PAH should not be treated without first performing a right heart catheterization.

6. Prognosis

Pulmonary arterial hypertension (PAH) is an independent risk factor for mortality among patients with systemic sclerosis (SSc) (Hachulla *et al.*, 2009). The severity of the PAH and the presence of coexisting interstitial lung disease (ILD) directly correlate with mortality (Condliffe *et al.*, 2009; MacGregor *et al.*, 2001; Mukerjee *et al.*, 2003; Mathai *et al.*, 2009):

- A prospective cohort study of 794 patients with SSc found a prevalence of PAH of 12 percent, which was confirmed by right heart catheterization (Mukerjee *et al.*, 2003). The two year mortality rates among patients with mean pulmonary artery pressures of < 32 mmHg and > 45 mmHg were 22 and 61 percent, respectively. A high right atrial pressure (indicative of right ventricular failure) was the strongest hemodynamic predictor of mortality.

- A prospective cohort study of 59 patients with SSc and pulmonary hypertension (confirmed by right heart catheterization) compared patients with coexisting ILD to patients without ILD. Survival was significantly worse among patients with coexisting ILD (46 versus 79 percent). Most deaths among the patients with ILD are due to respiratory failure, whereas most deaths among patients without ILD are due to right heart failure. (Mathai *et al.*, 2009)

Progression of SSc-associated PAH is not inevitable. In one observational study of patients with SSc, 30 percent of those who had an estimated pulmonary artery pressure of >30 mmHg on an echocardiogram were found to have an estimated pulmonary artery pressure <30 mmHg two years later.

The prognosis for patients with SSc-associated PAH is worse than that for patients with idiopathic pulmonary arterial hypertension (IPAH). This was suggested by a retrospective cohort study of 91 patients that found that patients with SSc-associated PAH had one-, two-, and three-year survival rates of 87, 64, and 64 percent, respectively. In contrast, patients with IPAH had one-, two-, and three-year survival rates of 91, 88, and 78 percent, respectively. Patients with SSc-associated PAH also had higher serum levels of N-terminal brain natriuretic peptide (NT-BNP) than patients with IPAH. NT-BNP is an index of cardiac strain. (Fisher *et al.*, 2006; Mathai *et al.*, 2010)

Survival among patients with SSc-associated PAH appears to have improved modestly over the past decade. This is most likely the consequence of earlier diagnosis and more effective supportive and directed therapies. A prospective cohort study of 92 patients with SSc-associated PAH (confirmed by right heart catheterization) compared the survival of patients prior to 2002 with that of patients in the current treatment era (Williams *et al.*, 2006). Two year survival was significantly better in the current era (71 versus 47 percent). Therapy generally consisted of diuretics, digoxin, oxygen, warfarin, and prostanoids prior to 2002, but the endothelin-1 antagonists became the most frequently used first-line therapy during the current era.

Despite its improvement, the mortality rate of SSc-associated PAH remains unacceptably high, particularly when associated with ILD.

7. Treatment

PRIMARY THERAPY – Primary therapy of pulmonary hypertension refers to treatment that is directed at the underlying cause. In the case of systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH), primary therapy refers to treatment of the SSc.

There are no established, disease-modifying therapies for SSc. However, there are effective treatments for many of its organ-based complications. The indications for the treatment of these complications are reviewed separately.

DIRECTED THERAPY – Directed therapy targets the pulmonary arterial hypertension (PAH), rather than the cause of the PAH. It is administered by clinicians with expertise in the evaluation and management of patients with pulmonary hypertension. Most aspects of directed therapy for patients with systemic sclerosis (SSc)-associated PAH are identical to those for patients with other types of PAH:

- Directed therapy is indicated for patients whose PAH is symptomatic, defined as a World Health Organization (WHO) functional class of II, III, or IV (table 1).
- Right heart catheterization is performed prior to the initiation of directed therapy in order to confirm the PAH and assess its severity.
- Classes of drugs approved for directed therapy include endothelin-1 antagonists, phosphodiesterase type 5 inhibitors, and prostanoids. (Hassoun, 2009)
- The preferred agent depends upon the severity of functional limitation, clinician preference, and patient preference.

The clinical outcomes of directed therapy in patients with SSc-associated PAH are the focus of this section. An important caveat to consider when appraising the evidence is that most trials used the six-minute walk test (6MWT) as the primary outcome. While this may be a reasonable surrogate outcome for patients with idiopathic pulmonary arterial hypertension (IPAH), it has not been validated as a reliable tool for evaluating the severity of pulmonary hypertension and the response to therapy in patients with SSc-associated PAH. (Impens *et al.*, 2008; Kowal-Bielecka *et al.*, 2010)

Endothelin-1 receptor antagonists – Endothelin-1 receptor antagonists can be either non-selective, blocking signaling mediated by type A and type B endothelin-1 receptors, or selective, blocking signaling mediated by only type A endothelin-1 receptors.

Nonselective – Bosentan is a non-selective endothelin-1 receptor antagonist. The following evidence suggests that bosentan is beneficial in SSc-associated PAH, although the response may be less than that in IPAH:

- The multicenter BREATHE-1 trial randomly assigned 213 patients with PAH (approximately 30 percent of whom had SSc- or systemic lupus erythematosus [SLE]-associated PAH) to receive bosentan or placebo (Rubin *et al.*, 2002). The patients with SSc- or SLE-associated PAH who received bosentan had an increase in their 6MWT of 3 m, while those who received placebo had a decrease of 40 m (mean difference 43 m). In comparison, patients with IPAH who received bosentan had an increase in their 6MWT of 46 m, while those who received placebo had a decrease of 5 m (mean difference 51 m). Patients with SSc- or SLE-associated PAH who received bosentan also had delayed progression to clinical worsening compared those treated with placebo. So, it is clearly seen that bosentan prevented deterioration of the 6MWT in the scleroderma subgroup.
- In a study of 53 patients who had PAH associated with either SSc- or scleroderma spectrum disorder, bosentan therapy was associated with a 48-week survival of 92 percent (Denton *et al.*, 2008). This exceeds that of historical controls, which had estimated two year survival rates of only 50 percent. (Koh *et al.*, 1996; Kawut *et al.*, 2003)

Selective – Ambrisentan and sitaxsentan are selective type A endothelin-1 receptor antagonists. Ambrisentan is available in the United States. Sitaxsentan is not yet available in the United States, but is available in Europe. The evidence suggests that both are beneficial in patients with SSc-associated PAH, although the response may be less than that in IPAH:

- The multicenter ARIES-1 and ARIES-2 trials randomly assigned 394 patients with PAH to receive either ambrisentan or placebo (Galiè *et al.*, 2008). The 6MWT improved among all patients at 12 weeks, including patients with SSc- or connective tissue disease-associated PAH. However, those with SSc- or connective tissue disease-associated PAH had a more modest response (mean difference 15 to 23 m) when compared to patients with IPAH (mean difference 50 to 60 m).

- A post hoc subgroup analysis compared sitaxsentan to placebo in 42 patients with connective tissue disease-associated PAH, using data from an earlier randomized trial (Girgis *et al.*, 2007; Barst *et al.*, 2004). The subgroup analysis found that the sitaxsentan group had an increase in their 6MWT of 20 m, while the placebo group had a decrease of 38 m (mean difference 58 m). Patients with SSc who received sitaxsentan also had a delay in clinical worsening.

The poor therapeutic response of SSc-associated PAH, compared with other types of PAH, may reflect the multisystemic nature of SSc, the frequent involvement of the heart and lungs, and/or differences in vascular pathogenesis.

Phosphodiesterase type 5 inhibitors – The phosphodiesterase type 5 (PDE-5) inhibitors reduce the catabolism of cGMP, enhancing the pulmonary vasodilatation induced by endogenous nitric oxide. Sildenafil and tadalafil are the PDE-5 inhibitors that have been approved for the treatment of PAH.

- Sildenafil – The effects of sildenafil were demonstrated by the multicenter SUPER-1 trial, which compared three doses of sildenafil (20, 40, or 80 mg three times daily for 12 weeks) to placebo in 278 patients with symptomatic PAH (Galiè *et al.*, 2005). A subgroup analysis of 84 patients with SSc- or connective tissue disease-associated PAH detected improvement in the 6MWT, New York Heart Association (NYHA) functional class, pulmonary artery pressure, and pulmonary vascular resistance among those treated with sildenafil at a dose of 20 mg three times daily (Badesch *et al.*, 2007). There was no dose-response gradient in this group (different than patients with IPAH). The long-term effectiveness of sildenafil in SSc-associated PAH has not been reported.
- Tadalafil – Tadalafil has the advantage of being administered once daily. However, its efficacy in the treatment of connective tissue disease-associated PAH has not been evaluated.

Prostanoids – The prostanoids were the first agents shown to improve symptoms, functional ability, and hemodynamic parameters of patients with SSc-associated PAH (Badesch *et al.*, 2000). Formulations include epoprostenol, treprostinil, and iloprost.

Epoprostenol – The following studies illustrate the short-term and long-term efficacy of epoprostenol:

- The short-term efficacy of continuous intravenous epoprostenol in SSc-associated PAH was demonstrated by a randomized trial of 111 patients. The mean pulmonary artery pressure decreased 10 percent among patients treated with epoprostenol, compared to an increase of 2 percent among those who received placebo. In addition, epoprostenol therapy decreased pulmonary vascular resistance, increased cardiac output, and improved the functional class.
- The long-term benefits of continuous intravenous epoprostenol in SSc-associated PAH are uncertain due to methodological limitations of the relevant studies. An analysis of data from the original epoprostenol trial and its open-label extension study found one-, two-, three-, and four-year survival rates of 71, 52, 48, and 48 percent, respectively, among patients with SSc-associated PAH (Badesch *et al.*, 2009). These survival rates are better than those of historical controls.

Treprostinil – Treprostinil is a stable prostacyclin analogue that can be administered by either continuous intravenous infusion or subcutaneous infusion using a portable microinfusion pump (similar to an insulin pump). Inhaled treprostinil has been developed, which can be administered by only four inhalations daily. (Voswinckel *et al.*, 2009)

In a randomized trial that compared subcutaneous treprostinil to placebo, a subgroup analysis of 90 patients with SSc- or connective tissue disease-associated PAH found that treprostinil was associated with improved dyspnea, cardiac index, and pulmonary vascular resistance (Oudiz *et al.*, 2004). The treprostinil group also had an improved 6MWT, but the effect was modest (mean difference 25 m).

Iloprost – An inhaler that produces aerosol particles small enough to ensure alveolar deposition delivers Iloprost. The usual formulation requires as many as nine daily doses because of its relatively short duration of action, with each dose requiring 10 to 15 minutes. A newer, more concentrated formulation still requires 6 to 9 inhalations daily, but each dose requires less time.

The effect of iloprost was demonstrated by an open-label, uncontrolled trial of five patients with SSc-associated PAH (Launay *et al.*, 2001). Iloprost therapy was associated with an increased 6MWT (85 m) at six months.

SUPPORTIVE THERAPY – Supportive therapy targets the sequelae of the pulmonary arterial hypertension (PAH) and should be considered in all patients who have systemic sclerosis (SSc)-associated PAH. It includes supplemental oxygen for patients with resting or exercise hypoxemia and diuretics for patients with fluid retention.

SSc-associated PAH is not one of the widely accepted indications for anticoagulation. However, anticoagulation may be considered on a case-by-case basis after carefully weighing the potential benefits of fewer potential thromboembolic complications against the risk of bleeding.

LUNG TRANSPLANTATION – Lung transplantation remains an option for suitable operative candidates who have severe symptoms due to systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH) and have failed to respond to intravenous epoprostenol, either alone or in combination with other agents.

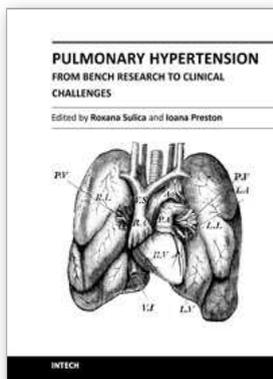
The morbidity and mortality of lung transplantation in patients with SSc-associated PAH does not appear to be significantly different from that of patients undergoing lung transplantation for idiopathic pulmonary fibrosis. This was illustrated by a retrospective study of 14 patients with SSc-associated PAH who had undergone lung transplantation (Schachna *et al.*, 2006). The two-year survival rate was 64 percent.

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The textbook "Pulmonary Hypertension - From Bench Research to Clinical Challenges" addresses the following topics: structure and function of the normal pulmonary vasculature; dysregulated cellular pathways seen in experimental and human pulmonary hypertension; clinical aspects of pulmonary hypertension in general; presentation of several specific forms of pulmonary hypertension, and management of pulmonary hypertension in special circumstances. The textbook is unique in that it combines pulmonary and cardiac physiology and pathophysiology with clinical aspects of the disease. First two sections are reserved for the basic knowledge and the recent discoveries related to structure and cellular function of the pulmonary vasculature. The chapters also describe dysregulated pathways known to be affected in pulmonary hypertension. A special section deals with the effects of hypoxia on the pulmonary vasculature and the myocardium. Other three sections introduce the methods of evaluating pulmonary hypertension to the reader. The chapters present several forms of pulmonary hypertension which are particularly challenging in clinical practice (such as pulmonary arterial hypertension associated with systemic sclerosis), and lastly, they address special considerations regarding management of pulmonary hypertension in certain clinical scenarios such as pulmonary hypertension in the critically ill.

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