# Pulmonary Hypertension Complicating Connective Tissue Disease

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Semin Respir Crit Care Med 2013;34:581–599.

## Abstract

Pulmonary hypertension (PH) may complicate connective tissue disease (CTD), particularly systemic sclerosis (SSc, scleroderma), and markedly increases mortality. More than 70% of cases of PH complicating CTD occur in SSc, which is the major focus of this article. Pulmonary complications (i.e., interstitial lung disease [ILD] and PH) are the leading causes of scleroderma-related deaths. "Isolated" PH (i.e., without ILD) complicates SSc in 7.5 to 20% of cases; secondary PH may also occur in patients with SSc-associated ILD. Several clinical markers and specific autoantibody profiles have been associated with PH in SSc. The role of PH-specific therapy is controversial, as prognosis and responsiveness to therapy are worse in SSc-associated PH compared with idiopathic pulmonary arterial hypertension. We discuss medical therapies for CTD-associated PH and the role of lung transplantation for patients failing medical therapy.

**Keywords**
- systemic sclerosis
- scleroderma
- pulmonary hypertension
- pulmonary arterial hypertension
- connective tissue disease

Pulmonary hypertension (PH) may complicate connective tissue disease (CTD), particularly systemic sclerosis (SSc),[1–6] systemic lupus erythematosus (SLE),[7–11] mixed connective tissue disease (MCTD),[5,6,8] and overlap syndrome.[5,7,12] Scleroderma accounts for the majority of cases of CTD-PH,[5] and will be discussed first.

## Systemic Sclerosis

Scleroderma (SSc) is a connective tissue disease characterized by microvascular damage, fibroblast activation, and excessive fibrosis of the skin, with varying degrees of visceral involvement (e.g., lungs, gastrointestinal [GI] tract, kidney, and heart).[13–17] Interstitial lung disease (ILD) complicates SSc in 21 to 60% of the patients[12–14,18–20]; and PH in 7.5 to 20% of the patients.[5,12,14,19,21–26] Pulmonary complications are the leading causes of scleroderma-related deaths.[14,27–29]

### Clinical Manifestations of Scleroderma

The diagnosis of SSc is based on the presence of dermatological manifestations (i.e., symmetrical skin or truncal sclerosis, skin ulcers, pitting scars, telangiectasias, calcinosis), internal organ dysfunction (e.g., esophageal dysmotility, pulmonary fibrosis (PF), PH, heart or renal aberrations), and autoantibody profile.[13–15] Raynaud phenomenon is present in $>$ 90% of patients with scleroderma and often is present for years before fibrosis appears.[13,14] Distinct SSc-associated autoantibodies define subsets of patients with scleroderma, with differences in clinical expression and prognosis[30–32] (discussed in detail later). Nailfold capillary microscopy can detect sclerodermatous microvascular damage via capillary loss, distortion, and dilatations, and correlates with extent of organ involvement.[33–35] Diagnostic criteria for SSc were proposed by the American College of Rheumatology (former American Rheumatism Association [ARA]) in 1980.[15] In 1988, LeRoy et al classified SSc patients into limited and diffuse

**Issue Theme** Current Challenges in Pulmonary Hypertension; Guest Editor, Marc Humbert, MD, PhD

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Tel: +1(212) 584-4662.

**DOI** http://dx.doi.org/10.1055/s-0033-1356547.
**ISSN** 1069-3424.

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subsets, with distinct differences in clinical expression and prognosis.[16] Subsequent refinements incorporating serum autoantibodies and nailfold capillary microscopy improved the sensitivity of the 1980 ARA criteria.[19,36] Scleroderma may be classified according to the extent of skin sclerosis.[14,16,35] This classification schema has been widely accepted and used in numerous clinical studies.[36] Limited cutaneous scleroderma (lcSSc), characterized by skin sclerosis of fingers (sclerodactyly) with or without mild sclerotic lesions involving neck, face, and armpits, is not usually associated with serious internal organ involvement.[14,16] Nonetheless, as will be discussed later, PH is more common in *limited* than diffuse SSc.[37,38] Diffuse cutaneous scleroderma (dcSSc), in which skin lesions are extensive (involving distal and truncal skin), is usually associated with serious visceral complications (particularly GI tract, ILD, renal, and heart)[14,16] and may progress rapidly.[13,37] The risk of developing renal crisis is higher in dcSSc than in lcSSc patients, with an odds ratio $> 7$.[39] As we will discuss later, dcSSc patients more frequently have autoantibodies against topoisomerase-1 (antitopoisomerase-1 [antitopo-1]) and have a worse prognosis than lcSSc patients.[14,16] A third subset, intermediate cutaneous scleroderma (icSSc) encompasses patients who typically have sclerosis of upper and lower limbs, neck, and face, *without* truncal involvement; the prognosis of icSSc is intermediate between lcSSc and dcSSc.[14,36] Rare SSc patients exhibit internal organ involvement *without* obvious cutaneous involvement (termed "sine scleroderma").[13,14,35,40] This classification scheme based upon extent of cutaneous involvement provides an overview of phenotype and prognosis, but marked variability exists even within these subsets.[14,36] Historically, the acronym CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) syndrome was used to define a subset of patients with SSc,[41] but some consider this term to be obsolete.[13] Approximately 10% of SSc patients have signs of other defined CTDs such as SLE, rheumatoid arthritis (RA), and polymyositis (termed "overlap syndrome").[12]

## Epidemiology

SSc is rare (incidence 2.3–22.8 per million/y; prevalence, 88–280 per million).[13,14,42,43] More than 80% of SSc cases occur in females,[13,14,29,36] with a peak incidence between the age of 45 and 64 years.[14,36] Marked geographic variation in the prevalence of SSc has been noted.[42–45] SSc is more common in the United States (prevalence, 240 cases per million adults; incidence, 20 cases per million adults) than in Europe or Asia.[42,46–48] Cited prevalence rates per million adults were 158 in Paris[44] and 89 in the Netherlands.[26] In one analysis,[43] prevalence rates (per million) were: 276 (United States in 1990); 233 (Australia in 1999); 158 (France in 2001); and 88 (England in 2000). The incidence is increased among blacks, but no other significant differences in distribution have been documented.[13,14,42,49] Clusters of SSc in families, Choctaw Indians, and other ethnic groups and differences in phenotypes among ethnic groups suggest a genetic component in at least some cases.[13,42,50] Further, scleroderma-associated polymorphisms of genes encoding cytokines, cytokine receptors, chemokines, and extracellular proteins have been reported.[13,50] Additionally, certain human leukocyte antigen (HLA) class II molecules have been linked to clinical phenotypes and specific autoantibodies.[13,51] "These data provide support for the notion that scleroderma is not one clearly defined disease but a syndrome encompassing various phenotypes."[13] Although, the etiology of SSc remains obscure, multiple factors have been suspected, including immune system alterations, genetic, exogenous, and toxic or infectious factors.[13,14,50]

## Prognosis

Scleroderma has the worst prognosis of the CTDs,[14,52] but the clinical expression and prognosis of SSc are widely heterogeneous.[13,14,16] Studies published in the "modern" era (after 1990), cite 10-year survival rates among patients with SSc ranging from 61 to 85%.[14,47,53–58] Involvement of visceral organs (principally lungs, kidneys, and heart) is the major factor determining prognosis.[13,14,29,37] The prognosis of dcSSc is much worse than lcSSc.[14,37] Ferri et al described 1,012 Italian SSc patients seen between 1955 and 1999.[14] Frequency of specific organ involvement at presentation and follow-up were: kidney (7 and 10%); heart (30 and 35%); lung (60 and 81%); and esophagus (60 and 68%).[14] In a cohort of 309 French-Canadians with SSc, the following organs were affected *at presentation*: kidney (2%); heart (9%); lung (24%); and esophagus (42%).[59] Criteria for specific organ involvement were not uniform among these studies.[14,59] Steen and Medsger evaluated 953 patients with *diffuse* SSc seen at the University of Pittsburgh from 1972 to 1995.[37] Severe organ involvement was defined as follows: (1) (kidney) renal crisis; (2) (heart) cardiomyopathy, symptomatic pericarditis, or arrhythmias requiring treatment; (3) (lung) radiographic PF and forced vital capacity (FVC) $< 55\%$ predicted; (4) (GI involvement) repeated pseudo-obstruction or severe problems requiring hyperalimentation; and (5) (skin) modified Rodnan skin score $> 40$. During follow-up, specific organ complications developed as follows: kidney (19%); heart (15%); lung (16%); GI tract (8%); and skin (24%).[37] It is important to note that most severe complications occurred within 3 to 4 years of presentation.[37]

PH and PF are the leading causes of death in SSc, accounting for 60% of the scleroderma-related deaths.[29] This contrasts with experience from the 1970s and 1980s when renal crisis was the leading cause of death in SSc.[37] The incidence of renal-related deaths fell dramatically following the use of angiotensin converting enzyme inhibitors in the 1980s among patients with renal crisis.[29,37,60] Investigators from the University of Pittsburgh evaluated scleroderma-related and all-cause deaths in a large cohort ($> 5{,}000$) of SSc patients seen from 1972 to 2001.[29] During that 30-year time frame, scleroderma-related deaths due to renal crisis fell from 42 to 6% whereas the proportion of scleroderma-related deaths due to PF or PH grew to 33 and 27%, respectively; deaths due to GI disease fell from 12 to 4%; and deaths due to scleroderma cardiac disease decreased from 10 to 5%.[29] A recent study from the EUSTAR (European League Against Rheumatism [EULAR] Scleroderma Trials and Research) database



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(inaugurated in June 2004) was remarkably similar.[61] The study prospectively followed 5,860 SSc patients from 151 centers; and out of which 284 patients (5.2%) died. The attributable causes of SSc-related deaths included: PF (35%); PH (26%); cardiac (26%); renal (4%); and GI tract (3%).

Reported scleroderma survival rates from different countries vary widely.[12,14,19,28,53–55,57,59,62–64] Differences between regional cohorts in part may reflect different phenotypes, autoantibodies, and clinical expression of the disease[19,59,65] rather than differences in therapy. In a large Italian cohort of SSc patients ($n = 1{,}012$) seen between 1955 and 1999, 10-year survival rates were 60.6% for patients recruited between 1955 and 1985 and 76.8% for patients recruited between 1986 and 1999.[14] Factors associated with a higher mortality included: male gender, lung, heart or kidney involvement, older age, antitopo-1 or U1 autoantibodies.[14,45] Among patients with lcSSc, icSSc, and dcSSc, 10-year survival rates were 78.3, 65.5, and 52.2%, respectively. The most frequent causes of death were cardiac (36%), pulmonary (24%), and cancer (15%).[14] Shorter duration of Raynaud phenomenon at the disease onset correlated with a worse survival.[14] A meta-analysis of seven medical centers in the United States, Europe, and Japan evaluated all-cause mortality in a cohort of 1,645 incident cases of SSc.[28] By multivariate analysis adjusted for age and sex, four factors were associated with heightened mortality risk: renal involvement (hazards ratio [HR], 1.9); heart involvement (HR, 2.8); pulmonary involvement (HR, 1.6); antitopo-1 antibodies (HR, 1.3).[28] Esophageal involvement was not associated with mortality. In a cohort of 496 Japanese patients with SSc, survival rates at 5 and 10 years were 93.7 and 82%, respectively.[47] Factors associated with a poor prognosis included: antitopo-1 antibody and *absence of* anticentromere antibody (ACA).[47] A study of 309 French-Canadians with SSc from 1984 to 1999 cited 5- and 10-year survival rates of 91.7 and 79% for lcSSc and 78.6 and 62.4% for dcSS, respectively.[59] Scleroderma was the primary cause of death in 35 out of 66 (53%) deaths. Organ-specific cause of SSc-related deaths included: renal failure (20%); PH (11.4%); cardiac (11.4%); primary biliary cirrhosis (11.4%); small intestinal involvement (8.5%); and PF (5.7%). By multivariate analysis, skin involvement of the trunk, age, diffusing capacity for carbon monoxide ($DL_{CO}$) $\leq$ 70% predicted, increased sedimentation rate ($\geq$ 25 mm/h), and hemoglobin $<$ 12.5 g/dL independently predicted mortality. Another Canadian study of 237 patients with SSc between 1979 and 1990 cited 3-, 6-, and 9-year survival rates of 86, 76, and 61%, respectively.[54] Renal, cardiac, pulmonary disease, or older age were associated with a reduced survival. PH was the most common cause of SSc-related death; 28% of deaths were unrelated to SSc (particularly cancer and ischemic cardiac disease).[54] A Swedish series of 249 SSc patients cited 5- and 10-year survival rates of 86 and 69%, respectively.[56] Among the 49 deaths, 24 were due to pulmonary complications (PF, PH, pneumonia, or lung cancer).[56] In a cohort of 178 Danish patients with SSc, the following factors were associated with increased mortality: PF; renal or cardiac involvement; dcSSc; topo-1 or ribonucleic acid polymerase (RNAP) antibodies.[55] Cox regression analysis cited the following risk factors for mortality: right heart failure (relative risk [RR], 12.4); dcSSc (RR, 7.8); nephropathy (RR, 6.1); $DL_{CO}$ $<$ 40% (RR, 4.0).[55] In an Australian cohort of 177 patients from 1953 to 1983, survival rates correlated with extent of cutaneous involvement.[64] A 10-year survival rate was 71% for patients with sclerodactyly *only*; 58% with skin stiffness proximal to the metacarpophalangeal joints; 21% with diffuse scleroderma involving the trunk.[64] In a Spanish cohort of 79 patients with SSc, 15-year survival was 62%.[53] Factors associated with increased mortality by multivariate analysis included: age at onset $>$ 60 years; FVC $<$ 70%; renal crisis.[53] In a cohort of 2,940 SSc patients in the EUSTAR database, risk factor for mortality by multivariate analysis included: proteinuria: PH; FVC $<$ 80%; dyspnea on exertion; reduced $DL_{CO}$; older age at SSc onset; and skin thickness.[61]

Severe organ involvement (i.e., renal crisis, cardiac, lung, GI tract) in patients with dcSSc typically occurs early in the course of the disease (first 3 years), and was associated with a poor cumulative 9-year survival rate (38%) compared with 72% in patients *without* such involvement ($p < 0.001$).[37] Renal crisis usually occurs during the first 4 years of the disease in SSc patients who develop this complication.[37,66] Similarly, among scleroderma patients with severe lung disease; the greatest loss of lung function occurred during first 2 years of the disease.[18]

## Scleroderma Autoantibodies

SSc-related autoantibodies are present in $>$ 85% of patients with scleroderma; the most common are ACA (present in 40–70%) and antitopo-1 (formerly anti-Scl-70), found in 12 to 40%, but prevalence varies widely.[13,14,24,30,40,48,59,65,67,68] Importantly, ACA and antitopo-1 are almost mutually exclusive.[14,30,31,67,69,70] Several additional antinucleolar antibodies (ANoA) have been detected in SSc patients.[14,30,31,71] These ANoA include: RNAP I, II, and III[31]; small nuclear ribonucleoproteins (snRNP)[71]; U3 snRNP (fibrillarin)[30,72]; U1 snRNP[71]; Th/To (7–2 RNA)[73]; PM-Scl (C1D, PM-Scl-100, PM-Scl-75 proteins)[30,74]; human upstream binding factor (hUBF, formerly anti-NOR 90)[30,75]; Ku[30,76,77]; U11/U12RNP[78]; and histones.[71] Additional autoantibodies in some patients with SSc include: endothelial cell (EC) antibodies[79,80]; antiphospholipid/anticardiolipin antibodies[81]; autoantibodies to the platelet-derived growth factor (PDGF) receptor.[82] ANoA-positive patients may also have circulating serum antitopo-1 or ACA.[14]

## Influence of Autoantibody Type on Clinical Features and Prognosis

Specific autoantibodies define clinical subsets of SSc.[14,30,32,67] In a sentinel study from the University of Pittsburgh, ACA and antitopo-1 (anti-Scl-70) were measured in a cohort of 397 consecutive SSc patients.[67] Overall, 22% had ACA and 26% had anti-Scl-70. Importantly, no patient had *both* ACA and anti-Scl-70 antibodies.[67] ACAs were almost exclusively found in lcSSc (96%) and were associated with calcinosis and telangiectasias. By contrast, anti-Scl-70 was more common in dcSSc and was associated with peripheral vascular disease (pitting scars) and PF.[67] Subsequent studies



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confirmed that ACA is more common in limited SSc and has a better prognosis whereas antitopo-1 is more common in diffuse SSc and is often associated with PF.[14,30,63,68,71,74,83] In an Italian study comprising of 1,012 SSc patients, ACA was present in 53% of patients with limited, 21.8% with intermediate, and 11.3% of patients with diffuse SSc.[14] Conversely, antitopo-1 was present in 25.3% of patients with limited, 51.3% with intermediate, and 58.6% of patients with diffuse SSc.[14] In a French-Canadian study, ACAs were present in 50% of patients with limited or sine scleroderma, 34.6% in the intermediate group, and 3.4% in diffuse SSc, respectively.[59] By contrast, the frequency of antitopo-1 without ACA was similar in limited (10.5%), intermediate (12.8%), and diffuse SSc (13.8%).[59] In some studies, antitopo-1 antibodies have been associated with peripheral vascular disease,[63,67] malignancy,[32] peripheral neuropathy,[83] cardiac disease,[32] and renal crisis.[84] Antitopo-1 has been associated with the worst prognosis among autoantibodies[30,36,47] whereas several studies cited better survival in ACA-positive patients.[14,47,63,67,85] A seminal study of SSc patients detected antibodies to RNAP III in 45% of patients with dcSSs but in only 6% of lcSSc and 0% with SSc overlap syndrome.[86] Anti-RNAP III correlated with statistically higher mean maximum skin thickness scores but a lower incidence of telangiectasias, inflammatory myopathy, restrictive lung disease, or serious cardiac manifestations compared with SSc patients with antitopo-1.[86] Thus, anti-RNAP III may be a marker of extensive cutaneous SSc.

Additional clinical subsets have been observed with specific antibodies. Clinical links with autoantibody status included: anti-U3RNP and RNAP (dcSSc and systemic disease) [30,74]; anti-U3snRNP (dcSSc, myositis and isolated PH)[72]; anti-RNAP III (dcSSc and renal involvement; low incidence PF, myopathy, or cardiac manifestations)[86,87]; anti-U1snRNP (lcSSc; joint inflammation; SSc-myositis overlap; isolated PH; less renal involvement)[30]; anti-U11/U12RNP (Raynaud phenomenon; PF)[78]; anti-Ku (myositis; arthritis; joint contractures)[76,77]; anti-PM-Scl (SSc-myositis overlap, myositis, arthritis, lcSSc)[30,88]; anti-Th/To (isolated PH, lcSSc and renal crisis)[73]; anti-Th/To and anti-PM-Scl (lcSSc)[30,74]; anti-hUBF (lcSSc, mild internal organ involvement; favorable prognosis) [75]; EC antibodies (digital infarcts; PH)[79,80,89]; antiphospholipid antibodies (thrombosis, PH)[81,90]; antiphosphatidyl-serine prothrombin complex (peripheral ischemia, PF, and PH).[91] Recently, SSc patients with (+) PM-Scl autoantibody ($n = 76$) were compared with 2,349 SSc patients *without* PM-Scl.[92] PM-Scl-70 (+) patients were younger, more often exhibited overlap with another CTD (particularly PM or DM), had more frequent limited cutaneous involvement, more skeletal muscle involvement, radiographically evident PF, calcinosis, and less PH (5 vs. 15% for PM-Scl-70 (−) patients). Importantly, 10-year survival among PM-Scl-70 (+) patients was 91 versus 65% for PM-Scl-70 (−) patients ($p = 0.0002$). A recent multicenter study examined 802 sera from Canadian SSc patients for autoantibodies ACA and centromeric proteins (CENP)-A and CENP-B.[93] Autoantibodies were present as follows: ACA (35%); CENP-A (34%); CENP-B (36%); RNAP-III (19%); and antitopo-1 (16%). There was a considerable overlap among ACA, CENP-A, and CENP-B autoantibodies. Of 301 patients (+) for any of these three antibodies, 86% were positive for all three. By contrast, overlap among antitopo-1 or RNP-III and ACA, CENP-A or CENP-B was low (around 1%). Clinical characteristics of ACA, CENP-A, and CENP-B (+) patients were similar and included: older age; less skin involvement; more PH; less ILD; less renal crisis; less myositis compared with the remainder of the cohort.

Certain autoantibodies have been more common in SSc patients with PH including: antifibrillarin antibodies (anti-U3-RNP)[72]; fibrin-bound tissue plasminogen activator in CREST patients[94]; antitopoisomerase II-α antibodies, particularly in association with HLA-B35 antigen[95]; antiendothelial cell IgG antibodies.[79,96] In some studies, ACA was associated with PH[30,68,71,73] but this is not consistent.[36] IgG antiendothelial antibodies were associated with a significantly higher incidence of digital infarcts and gangrene and PH in SSc patients.[79] These antibodies were more common in diffuse (40%) than limited (13.5%) SSc.[79] A study from the United Kingdom consisting of 393 patients with lcSSc cited a relatively high incidence of PH in patients with anti-Th/To (28%) and ACA (19%) antibodies.[73] Certain autoantibodies (anti-U1-RNP and anti-dsDNA) upregulate adhesion molecules and HLA class II molecules on human pulmonary ECs,[97] and may promote an inflammatory pulmonary vasculopathy. Furthermore, Ig antibodies directed against fibroblasts are present in sera of patients with idiopathic pulmonary arterial hypertension (IPAH) and SSc-PH,[96,98] and may contribute to release of cytokines and growth factors that may contribute to the pathogenesis of vascular remodeling in PH.[99]

### Genetic Factors

Ethnic and genetic factors may influence the incidence of SSc, clinical features, disease expression, and autoantibody status.[18,49,65,100,101] The severity of disease and mortality is worse among black SSc patients.[18,101] In one study of patients with SSc, PH was more common in African–Americans compared with Hispanics or Caucasians.[49] Kuwana et al reported a lower frequency of PF and better cumulative survival in white as compared with black and Japanese patients.[65] The role of genetic mutations has been recognized in idiopathic and familial PH.[102] Little is known about the genetic involvement in SSc-PH. Mutations in the bone morphogenetic protein receptor-2 (often found in IPAH),[103] were not detected in two small cohorts of SSc-PH.[104,105] Wipff et al reported an association between endoglin gene polymorphism and SSc-PH as compared with SSc patients *without* PH or controls.[106] Additional studies are required to determine the role of genetic factors or polymorphisms and SSc-PH.

## Pulmonary Hypertension in Systemic Sclerosis

### Pathology of Systemic Sclerosis Pulmonary Hypertension

Pathological features of SSc-PH are similar to the pulmonary arterial/arteriolar lesions observed in IPAH, but may



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also display fibrous remodeling of the pulmonary venous system, with occlusive lesions in veins/preseptal venules (resembling pulmonary venoocclusive disease [PVOD]), and capillary angioproliferation and postcapillary congestion (►**Fig. 1A–F**).[107,108] Plexogenic vasculopathy, which is not uncommon in IPAH, was never observed in SSc-PH.[107,108] Isolated cases of scleroderma patients with PVOD and pulmonary capillary hemangiomatosis (PCH) [109,110] have been described. Obstructive lesions within pulmonary venules may in part explain the poor responsiveness of SSc-PH to vasodilators. Additionally, an inflammatory component, with perivascular infiltrates, may be observed within the pulmonary vasculature in CTD-PH.[107]

## Pathogenesis of Pulmonary Hypertension in Systemic Sclerosis

Inflammation and autoimmunity likely play important roles in SSc-PH.[111,112] T- and B-lymphocytes, macrophages, dendritic cells, and leukocytes are found around the pulmonary vascular lesions in SSc-PH and IPAH.[111] Vascular changes noted in SSc included apoptosis,[113] EC activation, inflammatory cell recruitment, a procoagulant state,[114] intimal proliferation, and fibrosis leading to vessel obliteration.[111] Endothelial injury occurs in SSc, with increased levels of soluble cell adhesion molecules[111] and circulating vascular endothelial growth factors.[115] Italian investigators cited elevated serum levels of seven angiogenic factors in a cohort of

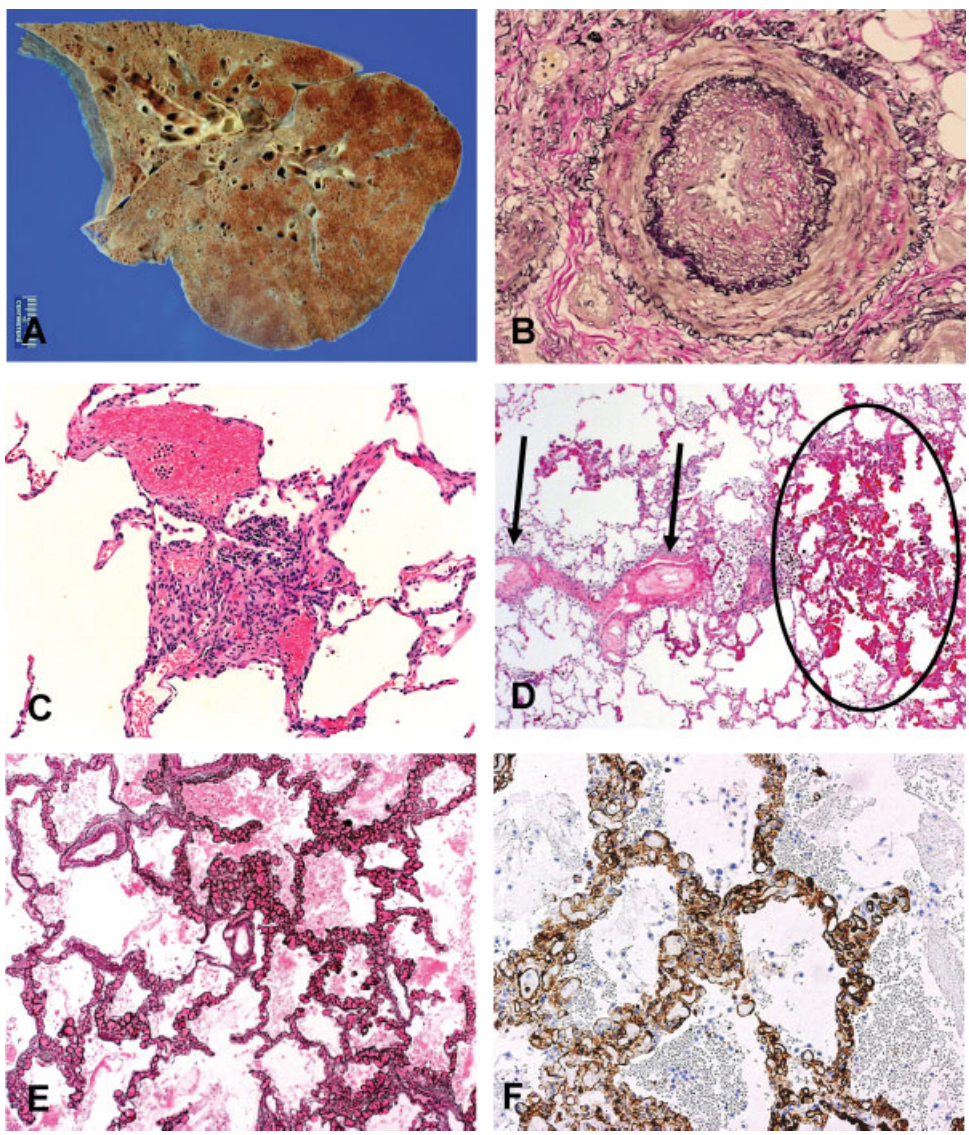


**Fig. 1** Vascular changes in "scleroderma lung." (A) Gross lung with interstitial fibrosis in a UIP pattern; (B) typical arterial lesion with medial hypertrophy and intimal fibrosis (EVG stain, x100); (C) plexiform/angiomatoid lesion that has been described in progressive systemic sclerosis (PSS) but is rare in our experience (H&E stain, x100); (D) pulmonary venous occlusive disease (arrows) and pulmonary capillary hemangiomatosis (PCH, oval), often seen together when present in PSS (H&E, x40); (E) PCH demonstrated by reticulin stain (x40); and (F) PCH demonstrated by CD34 immunohistochemistry (x100). CD, cluster of differentiation; EVG, elastic-Van Gieson; H&E, hematoxylin and eosin; UIP, usual interstitial pneumonia.

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patients with SSc; specific molecules correlated with clinical subsets.[116] Higher levels of PDGF-BB and platelet endothelial cellular adhesion molecule-1 (PECAM-1) were observed in patients with digital ulcers while lower levels of PECAM-1 were found in SSc patients with PH. Additionally, interleukin-8 levels were higher in PH but lower in ILD. A variety of autoantibodies in SSc-PH may influence the pulmonary vascular lesions. Autoantibodies can upregulate adhesion molecules and human pulmonary arterial EC,[97] leading to proliferative vasculopathy. Anti-EC antibodies may activate EC, induce the expression of adhesion molecules, and trigger apoptosis.[117] Serum antibodies to fibroblasts have been detected in patients with SSc-PH and IPAH,[99] and can activate fibroblasts and induce collagen synthesis. Increased levels of growth differentiation factor 15 (GDF 15) protein, a member of the transforming growth factor-β family, were noted in plasma and lung tissue from patients with SSc-PH.[118] Importantly, plasma GFD15 levels correlated with right ventricular systolic pressure (RVSP) by echocardiogram and FVC/$DL_{CO}$ ratio and were associated with decreased survival. In summary, multiple autoantibodies and proinflammatory/profibrotic cytokines may be involved in the pathogenesis of SSc-PH. These effects may in part be mediated or modulated by genetic mutations, candidate genes, or polymorphisms, but little is known regarding the role of genes in the pathogenesis of SSc-PH.

## Diagnosis of Pulmonary Hypertension in Systemic Sclerosis

Right heart catheterization (RHC) remains the gold standard for the diagnosis of PH[119,120] and assessment of prognosis.[121,122] Baseline resting hemodynamic data (particularly right atrial pressure [RAP], cardiac index [CI], and pulmonary vascular resistance [PVR]) are predictive of severity of disease and prognosis in IPAH[121] but are less predictive of clinical evolution of the disease in SSc-PH.[111,123] Furthermore, RHC is invasive and not well suited for serial monitoring of the course of the disease. In this context, noninvasive techniques such as Doppler echocardiography (DE),[6] N-terminus pro-brain natriuretic peptide (N-TproBNP),[23,124] 6-minute walk test (6MWT),[125] and magnetic resonance imaging (MRI) [126,127] have been used.

DE is a good screening technique for suspected PH,[6,24,128] and may be useful for monitoring the course of the disease and response to therapy.[129] Elevated estimated RVSP, right ventricular (RV) dilation or dysfunction, and flattening of the interventricular septum are cardinal signs of PH.[119] Assessment of RVSP requires adequate visualization of the tricuspid regurgitation jet, which is possible in $< 70\%$ of cases.[119,130] Other parameters to assess PH include the Tei index,[131] tricuspid annual peak systolic velocity,[132] and tricuspid annual plane systolic excursion.[133] Overall, DE is reliable in the presence of severe PH, but is not a sensitive marker of mild-to-moderate PH.[24,129] Furthermore, appropriate parameters and threshold ranges for the diagnosis (or exclusion) of PH have not been elucidated. RVSP $\geq$ 35 mm Hg is often used as a surrogate marker for PH. In one recent study from Thailand, 155 consecutive patients with SSc had DE; 26 were excluded because of an inadequate tricuspid regurgitant signal; 47 of 129 had RVSP $\geq$ 36 mm Hg.[134] Importantly, RVSP $\geq$ 36 mm Hg and the World Health Organization (WHO) class III/IV were associated with increased mortality (H.R., 2.22 and 4.27, respectively). Survival rates at 1-, 2-, and 3-years were 82, 78, and 67% in SSc patients with RVSP $\geq$ 36 compared with 98, 90, and 86% in SSc patients with RVSP $<$ 36. Patients did not receive PH-specific therapy. French investigators prospectively followed 384 SSc patients *without* PH at *initial* evaluation and without severe restriction by pulmonary function tests (PFTs) for a mean of 41.0 months.[24] DE criteria for proceeding with RHC included the following: peak velocity of tricuspid regurgitation (VTR) $\geq$ 2.8 m/sec in patients with *unexplained dyspnea* or VTR $\geq$ 3.0 m/sec in patients without dyspnea.[24] Using this algorithm, 26 patients (6.7%) underwent RHC. Eight had pulmonary arterial hypertension (PAH) by RHC; eight had postcapillary PH; two had PH associated with severe PF. Hence, the false (+) rate of DE was 30.7%.[24] Mukerjee et al prospectively evaluated DE and RHC in 137 patients with SSc (52 had concomitant PF).[129] Overall, 99 (73%) had PH by RHC. Estimated tricuspid gradient (TG) by DE showed a moderate positive correlation ($r^2 = 0.44$, $p < 0.005$) with mean pulmonary arterial pressure (mPAP) and TG as assessed by RHC.[129] A weak correlation between $DL_{CO}$ and mPAP by RHC was also found. Using a TG threshold $\geq$ 45 mm Hg on DE, sensitivity for PH by RHC was 58%; specificity, 97%. Lower TG thresholds were associated with unacceptably high false positive rates. However, no threshold could accurately exclude PH. Therefore, DE is a reasonable, albeit imperfect, screening approach to identify SSc patients with PH. Exercise DE[135,136] may improve sensitivity of DE, but its role in SSc has not yet been established. The combination of computed tomography pulmonary angiography (CTPA) plus DE may improve diagnostic accuracy over DE alone. In a cohort of 89 SSc patients with suspected PH, a composite index incorporating indices from CTPA and DE improved sensitivity; CTPA parameters correlated moderately well with pulmonary hemodynamics by RHC.[137]

Pulmonary functional parameters may be helpful in predicting PH. Investigators from the United Kingdom developed a formula to estimate mPAP noninvasively in a cohort of 386 SSc patients who had PFTs and RHC.[138] The equation was derived from the initial cohort of 257 patients, and validated in the next 129 patients. The derived equation was: (136 − percentage of oxygen saturation ($SpO_2$) (by oximetry) × $DL_{CO}$ percentage predicted = mPAP).[138] Using this equation to estimate mPAP, the prevalence rates of PH (by RHC) were as follows: $<$ 25 mm Hg, (4.4%); 25–35 mm Hg, (11.3%); $>$ 35 mm Hg, (62.9%). These investigators suggested that the combination of DE and this equation could better predict best candidates for RHC. Similarly, French investigators assessed 1,165 consecutive patients with SSc, and confirmed PH (by RHC) in 64 (5%).[139] Based on this derivation cohort, an equation ("Cochin risk prediction score [RPS]") was developed to predict the risk of developing PH using simple variables (age, FVC, $DL_{CO}$/alveolar volume [$V_A$]).[139] The validation cohort comprised 443 *without* PH at baseline, 20 of whom (4.5%) developed PH during follow-up (3 years).[139] The Cochin RPS score was remarkably accurate



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in assessing PH risk. Using a cutoff value of 2.72 for the Cochin RPS, patients at risk for developing PH during follow-up could be identified with 89.5% sensitivity and 74.1% specificity. Importantly, PH developed during follow-up in only 0.6% of patients in the lowest two quintiles, 1.7% in the 3rd and 4th quintiles, and 17.1% in the highest quintile ($p < 0.001$). Hence, simple demographic and PFT data could predict with reasonable accuracy which patients are likely to develop PH. European guidelines recommend annual screening of SSc patients (even asymptomatic) for PH using DE, but reserve screening for other CTDs only if pulmonary symptoms are present.[120] Other echocardiographic features may detect primary myocardial involvement (e.g., depression of left ventricular [LV] and RV systolic and LV diastolic function[140] or a restrictive mitral flow pattern in the absence of any other cardiopulmonary diseases).[141]

Elevated N-TproBNP concentrations are predictive of PH; serial levels may be helpful in gauging the course of the disease and assessing response to therapy. In one study, N-TproBNP levels, 6-minute walk distance (6MWD), and hemodynamic measurements were obtained in 109 patients with SSc, 68 of whom had PH documented by RHC.[124] Mean baseline N-TproBNP levels were markedly elevated in SSc patients with PH (1,474 pg/mL) compared with those *without* PH (139 pg/mL). A N-TproBNP level of 395 pg/mL predicted PH, with sensitivity of 56% and a specificity of 95%. Baseline N-TproBNP levels correlated with mPAP, PVR, and inversely with 6MWD. Importantly, elevated N-TproBNP at baseline or during follow-up were strongly correlated with mortality. French investigators prospectively followed 101 SSc patients who did *not* have PH or severe comorbidities for 3 years.[125] By multivariate analysis, baseline elevated N-TproBNP and $DL_{CO}/V_A$ ratio < 60% predicted development of PH during follow-up (H.R. 9.97 and 36.66, respectively). The combination of an increased NT-proBNP level together with a $DL_{CO}/V_A$ ratio of < 70% was highly predictive of PH during follow-up (H.R. 47.20). In another prospective study of 98 patients with PH (SSc-PH [$n = 55$]; IPAH [$n = 43$]), NT-proBNP levels were correlated with clinical and hemodynamic data.[142] NT-proBNP levels were higher in SSc-PH (3,419 pg/mL) than IPAH (1,393 pg/mL) ($p < 0.01$) and were more closely related to hemodynamics in SSc-PH than IPAH. Overall, 28 patients died. When stratified by group, NT-proBNP predicted survival in SSc-PH (H.R. 3.07, $p < 0.01$) but not in IPAP (H.R. 2.02, $p = 0.29$).

Pleural effusions on chest radiographs or CT scans may be a marker of RV dysfunction in PH patients.[143,144] In one study, 35/89 patients (39.3%) with CTD-PH had pleural effusions (including 23/51 (45.1%) with SSc).[143] In six cases, alternative explanations for pleural effusions were found. Among 29 pleural effusions without alternative explanation, 28 had right heart failure. When compared with patients *without* pleural effusions, the 29 patients with effusions had significant higher RAP (11.3 vs. 8.3 mm Hg, $p = 0.04$) and lower CIs (2.1 vs. 2.5, $p = 0.01$).

The 6MWT has been a key measure of prognosis and response to therapy in IPAH,[145] but this test has not been independently validated in SSc-PH.[146] The presence of concomitant musculoskeletal or joint involvement will reduce the reliability of the 6MWT in the assessment of SSc-PH.[147,148] However, given its ease, noninvasive nature, and low cost, 6MWT is useful to follow the course of the disease and assess response to therapy.

Cardiac MRI has a theoretical role to diagnose myocardial involvement in SSc,[126,127,149–151] and differentiate inflammatory, microvascular, and fibrotic components, but is expensive and its clinical value in assessing SSc-PAH has not been established.

## Epidemiology and Incidence of Systemic Sclerosis Pulmonary Arterial Hypertension

"Isolated" PH (i.e., *without* significant PF) complicates SSc in 7.5 to 20% of cases[3,21–26,111,152]; "secondary" PH may also occur in patients with SSc-associated PF (SSc-PF).[5,14,18,24] Two national studies estimated the prevalence of CTD-PH to be 2.3 and 10 cases per million in the general population.[153,154] A prospective study in the United Kingdom cited a prevalence/million population in 2006 of 4.23 for CTD-PH and 2.93 for SSc-PH.[5] A 3-year prospective study in France estimated the incidence of PH among SSc patients at 0.61 cases per 100 patient years (patients with severe restrictive lung disease or left heart disease were excluded).[24]

The precise incidence of PH is SSc has not been elucidated, as differing diagnostic criteria and patient populations have been examined. Autopsy series and clinical series in the 1960s and 1970s suggested a prevalence of over 60%,[155,156] but these represented the extreme end of the spectrum. Studies in the 1980s cited PAH in 9 to 33% of patients with SSc,[157,158] but these represented selected cohorts (often including patients at risk or suspected of having PH). Some studies utilizing DE in SSc patients cited prevalence rates of PH exceeding > 30%,[159,160] but diagnostic criteria for PH and patient selection were not uniform. Studies within the past decade have cited the prevalence of PH by DE among SSc patients ranging from 9.9 to 26.7%.[3,6,21,26,152,161,162] However, DE are not always reliable; prevalence rates were lower (7.85–12%) when RHC was required to substantiate the diagnosis of PH. In a prospective study of 722 patients with SSc followed for 4 years, 89 (12%) had PH confirmed by RHC.[21] In a prospective study of 21 medical centers in France, 599 patients with SSc without severe PF had DE ± RHC *if PH was suspected*.[23] The prevalence of PH confirmed by RHC was 7.85%. In a subsequent analysis of this cohort, 384 SSc patients *without* PH at initial evaluation were followed prospectively for a mean of 41 months.[24] During follow-up, precapillary PAH was confirmed by RHC in 8 patients (2.1%); 8 had postcapillary PH (2.1%); 2 (0.5%) had PH complicating severe PF.

Doppler echocardiograms are noninvasive, and can identify patients with possible PH, and elucidate the evolution of the disease process. A retrospective study in the United Kingdom from 1992 to 1997 assessed 930 SSc patients (dcSSc [$n = 295$]; lcSSc [$n = 635$]).[152] Serial DE were performed in 152 patients for whom "there was a clinical suspicion of" PH based on clinical exam, PFTs, chest radiographs, or CT scans. Overall, 13% had PH (defined as systolic pulmonary artery



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pressure [SPAP] > 30 mm Hg on DE). Wigley et al evaluated 791 patients with either SSc or MCTD from 50 community rheumatology practices in North America; 122 had known PH.[6] Of 669 patients who had not previously been evaluated for PH, 89 (13.3%) had estimated RVSP ≥ 40 mm Hg on DE (consistent with PH). Of these 89 patients, 82 (92.1%) had SSc; 7 (7.9%) had MCTD. Importantly, 27% of patients with RVSP ≥ 40 had severely reduced exercise capacity compared with 9.5% with RVSP < 40. The total prevalence of PH (by DE) in the survey was 26.7%. In a retrospective study at Johns Hopkins University, serial DE were performed in 457 SSc patients seen between 1990 and 2001.[162] PH was present in 96 of 457 (21%) of the *initial* DE. Among 361 with initial normal DE, 92 (26.0%) developed mild-to-moderate PH and 48 (13.6%) developed severe PAH during follow-up (median of 3.2 y). In multivariate analysis, the overall probability of severe PH rose to 27.3% if the patient had limited disease and was older than the median age (46.9 y) at the time of diagnosis.[162] Italian investigators performed exercise DE in 172 consecutive SSc patients in the New York Heart Association (NYHA) class I and class II and *normal* baseline DE and 88 healthy controls.[163] After exercise, SSc patients had statistically significantly higher SPAP and ΔSPAP/ΔCI compared with controls. The presence of ILD was an independent determinant of SPAP and ΔSPAP/ΔCI. The distribution of SPAP was normally distributed, whereas a bimodal distribution was evident in SSc. A subset of SSc patients (13%) exhibited peak SPAP > 48 mm Hg after exercise. These data suggest that exercise DE may identify patients at risk for developing PH, but this needs to be verified in prospective studies.

## Risk Factors for Pulmonary Arterial Hypertension in Systemic Sclerosis

Several clinical markers have been associated with an increased risk of PH in patients with SSc[17] including: limited skin involvement,[111,162,164,165] disease duration > 10 years,[111,166] late age of onset of SSc,[162] severity[167] or duration[165] of Raynaud phenomenon, reduced nailfold capillary density,[166,168] reduced $DL_{CO}$.[162,167,169] Certain autoantibodies (e.g., anti-U3 nucleolar ribonucleoprotein [U3snRNP][38,72] and ACA[30,68,71]) were associated with a higher incidence of PH in some studies.

Despite the generally poor prognosis of dcSSc, PH occurs infrequently in dcSSc (< 5%)[37,38]; most cases of PH occur in patients with lcSSc.[38,162,169] In a study from the University of Pittsburgh, 60 of 580 (10%) of patients with lcSSc and 14 of 677 (2%) with dcSSc developed isolated PH ($p < 0.001$).[38] Circulating antibodies to U3RNP were present in 6 of 13 (43%) patients with dcSSc *and* PH but in only 13 of 24 (6%) patients with dcSS *without* PH ($p < 0.001$).[38]

Reduced $DL_{CO}$ has been associated with an increased risk of PH in several studies.[6,162,169] In a cohort of 815 patients with SSc, 152 (19%) had an "isolated" reduction in $DL_{CO}$ < 55% predicted with a normal FVC.[169] In this subset, PH developed in 16 patients (11%). All patients who developed PH had lcSSc. Both $DL_{CO}$ < 55% predicted and FVC% predicted/$DL_{CO}$% predicted ratio > 1.4 correlated with PH.[169] Among subjects with FVC/$DL_{CO}$ ratio > 1.4, PH developed in 22% compared with 2% without elevated FVC/$DL_{CO}$ ratio. Follow-up PFTs were performed in 73 of 152 (48%) with initially low $DL_{CO}$. Only six patients developed severe pulmonary complications (PH in five; PF in one). In a 3-year prospective study of 101 SSc French patients *without* PH, 8 developed PH during that time frame.[125] By multivariate analysis, risk factors for PH included: $DL_{CO}/V_A$ ratio < 60% (H.R., 36.6) and elevated baseline NT-proBNP level (H.R., 9.97).[125] A retrospective study of 1,136 SSc patients in the United States cited older age, limited skin disease, and $DL_{CO}$ < 50% as risk factors for PH.[162] In that study, 316 patients *without* PH on initial DE were followed for a mean of 3.2 years. Overall, 25.5% developed mild-to-moderate PH (RVSP of 36–55 mm Hg) and 13.6% developed severe PH (RVSP ≥ 56 mm Hg) during that time frame. Of patients with mild-to-moderate PH initially, 17.7% progressed to severe PH and 15.6% regressed to normal. Among patients with severe PH, 25.0% regressed to mild-to-moderate PH and 3% normalized. The risk of developing PH over time increased dramatically when the $DL_{CO}$ was < 50% predicted.

## Prognosis of Systemic Sclerosis Pulmonary Hypertension

The presence of isolated PH markedly worsens prognosis in SSc (3-year survival approximating 50%)[2,5,21,27,111,123,124,152,170]; prognosis is even worse in the presence of concomitant PF.[3,5,111,171] PH remains the most common cause of death in patients with SSc,[27,111] and response to PH-specific therapy in SSc is poor.[5,111,112] Once *clinical symptoms* of PH occur, median survival is as low as 12 months.[170,172] The high mortality in part may reflect a higher prevalence of comorbidities in SSc-PH, including cardiac and pulmonary parenchymal involvement.[111,123]

The REVEAL (The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) study (comprising 54 centers) recently published the largest cohort of patients with PH confirmed by RHC in the United States (121 had IPAH; 641 had CTD-PH).[173] Patients in the CTD-PH group had better hemodynamics and DE compared with IPAH patients; however, BNP level and the prevalence of pericardial effusions were higher and 6MWD and $DL_{CO}$ were lower in the CTD-PH cohort. Importantly, 1-year survival was 86% in the CTD-PH group compared with 93% in IPAH ($p < 0.0001$). The 1-year survival was worse in SSc-PH (82%) compared with other CTD-PH diagnoses (SLE [94%]; MCTD [88%]; RA [96%]). Furthermore, patients with SSc-PH had lower $DL_{CO}$ and higher BNP levels compared with other CTDs. British investigators followed 315 new incidence cases of SSc-PH (confirmed by RHC) for a mean of 3.3 years.[5] The 1- and 3-year survival rates for "isolated" SSc-PH were 78 and 47%, respectively. However, among SSc patients with PF-associated PH, 3-year survival was only 28% ($p = 0.005$). Among patients with exercise-induced PH, only 5/42 (12%) died; however, 8 progressed to PH *at rest* by repeat RCH (at a mean of 838 days from diagnosis). By multivariate analysis, younger age, female sex, higher mixed venous $O_2$ saturation, and lower WHO functional class were independent predictors of survival.[5] Autoantibody status (ACA, antitopo-1, antinuclear antibody) did not influence survival. In another study from



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the United Kingdom, 89 patients with SSc-PH (confirmed by RHC) were prospectively followed.[21] Survival rates at 1-, 2-, and 3-years were 81, 63, and 56%, respectively. Predictors of mortality included: elevated mean right atrial presuure (mRAP [H.R., 21]); elevated mPAP (H.R., 20); low CI (H.R., 11).[21] Williams et al followed 109 patients with SSc (68 had PH documented by RHC; 41 had normal PA pressure) for a mean of 10 months (range, 1–18 mo).[124] The 1-year survival was 83.5% in those with PH compared with 100% *without* PAH. French investigators followed 546 subjects with SSc for a median of 37 months; patients with severe restrictive lung disease or left heart disease at baseline were excluded.[27] Of 47 patients with PH at baseline, 3-year survival was 56.3% compared with 94.4% in patients *without* PH at baseline. Importantly, prognosis is guarded even among patients with mild PH. Hachulla et al followed 12 SSc-PH (WHO class II) for a mean of 44 months; 8 progressed to class III or class IV and 2 died as a result of PH.[174] Published studies in the United States were small, single center studies, but consistently noted a worse survival with SSc-PH compared with IPAH.[123,170] Kawut et al reported 22 patients with SSc-PH and 33 with IPAH (confirmed by RHC) from the University of Pennsylvania.[170] The 1-year survival rates were 55% in SSc-PH and 84% in IPAH. The risk of death was higher in SSc-PH (H.R., 2.9); this increased mortality risk persisted after adjusting for a variety of demographic, hemodynamic, and treatment variables. In a cohort of 91 consecutive patients from Johns Hopkins University (SSc-PH [$n = 50$]; IPAH [$n = 41$]), 1- and 3-year survival rates were 88 and 48% in SSc-PH compared with IAPH (95 and 89%, respectively).[123] These mortality differences occurred despite lower mean PA pressures in SSc-PH (46.6 mm Hg) compared with IPAH (54.4 mm Hg) ($p = 0.02$); CIs were similar between cohorts (2.2 vs. 2.1 L/min/m$^2$, respectively).[123] Pericardial effusions and diastolic dysfunction were more common in SSc-PH patients. In previous studies, pericardial effusion was predictive of a poor outcome in SSc (independent of PH), and may be a manifestation of serositis and systemic inflammatory disease.[53,175] A retrospective study in the United Kingdom from 1992 to 1997 assessed 930 SSc patients (dcSSc $n = 295$; lcSSc $n = 635$).[152] Doppler echocardiograms were performed in 152 patients in whom "there was a clinical suspicion of" PH based on clinical exam, PFTs, chest radiographs, or CT scans. In these patients, serial DE was performed annually. Overall, 13% had PH (defined as SPAP on DE $>$ 30 mm Hg) on at least one occasion. Considerable fluctuation of SPAP measurements was noted on follow-up DE. SPAP remained stable during follow-up in one-third and fell in one-third. Patients with lcSSc were at substantially increased risk for rapid progression (only one with dcSSc progressed rapidly). In six patients, deaths was attributed to PH (six had lcSSc). Risk factors for increased mortality included: rapid progression; age $>$ 50 years; male gender.[152] Investigators from Johns Hopkins reported 76 consecutive patients with SSc-PH documented by RHC from 2000 to 2009.[176] Total 40 patients (53%) were in WHO class III or class IV. During a median follow-up of 36 months, 42 died; median survival was 4.01 years. Survival rates at 1, 3, and 5 years were 85, 67, and 36%, respectively. Multivariate analysis identified PVR, stroke volume index (SVI), and pulmonary arterial capacitance as strong predictors of survival. Interestingly, traditional hemodynamic parameters such as RAP, mPAP, and CI were not predictive of survival, after adjusting for WHO class. An estimated glomerular filtration rate $<$ 60 mL/min/1.73 m$^2$ portended a threefold risk of mortality.

Markers of worse prognosis in SSc-PH include male sex,[5] late age at diagnosis,[5] hyponatremia,[177] advanced WHO functional class,[5,178] reduced $DL_{CO}$,[171] reduced 6MWD,[21,178] elevated BNP,[124] impaired renal function,[176] concomitant ILD,[3,5,111,171] pericardial effusion,[123] and cardiac disease.[111] Sclerodermatous involvement of the heart may give rise to left ventricular dysfunction,[179] conduction defects,[179] arrhythmias,[141] pericardial effusions,[175] or myocardial fibrosis.[179] Pericardial effusion is threefold more common in SSc-PH compared with IPAH, and is a strong predictor of mortality.[27] Pericardial effusion can reflect increased right heart pressure[180] or the presence of serositis.[175] The ability of the RV to adapt to pressure overload may be compromised by myocardial inflammation and/or scarring.[179] Overbeek et al evaluated the relationship between mean RV pressure and stroke volume in patients with SSc-PH and IPAH.[181] Both groups had similar RAP and CI, but patients with SSc-PH exhibited lower stroke volumes for any given mean RV pressure, suggesting impaired RV contractility.

ILD and PF are common in diffuse SSc, and may independently cause PH.[167] The presence of ILD in SSc without PH shortens survival (median survival 5–6 y),[111] but survival is substantially worse among SSc patients with *both* ILD and PH.[3–5,21,171,182] Mathai et al reported 59 SSc patients with PH (20 had concomitant ILD).[171] Survival was significantly worse in the SSc-ILD cohort (1-, 2-, and 3-year survival rates of 82, 46, and 39%, respectively) compared with those without ILD (1-, 2-, and 3-year survival rates of 87, 79, and 64, respectively), $p < 0.01$.[171] By multivariate analysis, the presence of ILD was associated with a fivefold higher risk of mortality compared with lone PH. Type of initial PH therapy was not related to survival.[171] Data regarding PH-specific therapy for SSc patients with concomitant ILD and PH are limited.[111,171,183] However, Le Pavec et al retrospectively reviewed 70 SSc patients with PH and ILD who had RHC, 6MWD, and clinical assessment at baseline and at a mean of 7.7 months after initiation PH-specific therapy.[184] There was no change in 6MWD, WHO class, or hemodynamics with therapy. By multivariate analysis, only worsening oxygenation during follow-up and reduced renal function were risk factors for mortality. Survival rates at 1-, 2-, and 3-years were 71, 39, and 29%, respectively. These findings cast doubt on any benefit associated with PH-specific therapy in SSc-PH with concomitant ILD. Launay et al compared 47 SSc patients with PH and ILD with 50 SSc patients with "lone" PH.[182] The 3-year survival rates were lower in SSc-ILD (47%) compared with SSc-PH (71%), $p = 0.07$. In the ILD group, risk factors for mortality included pericardial effusion and lower $DL_{CO}$; interestingly, mPAP had no prognostic effect. French investigators evaluated 86 patients with dcSSc for a median of 72.5 months.[3] Overall, 52 patients (60%) had ILD (alone in 37); 18 had PH (alone in 3); 31 (36%) had no PH or ILD. Overall, 17

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patients died (19.8%). Nine of 18 (50%) patients with PH died whereas 8 of 68 (12%) *without* PH died ($p = 0.001$); 10 of 52 (19%) with ILD died, compared with 7 of 34 (21%) *without* ILD ($p = 0.99$). In the entire cohort, only age at diagnosis of SSc and PH were independent predictors of death (H.R., 1.06 and 4.09, respectively). Among patients with ILD, age at diagnosis of SSc and PH were again the only independent predictors of death (H.R., 1.07 and 5.07, respectively). Treatment with corticosteroids or immunosuppressive agents did not affect survival. Total 20 patients with ILD were treated with at least 6 cycles of monthly pulse intravenous (IV) cyclophosphamide (CYC); 8 had concomitant PH. SPAP worsened during CYC therapy but total lung capacity (TLC) did not change.

## Pulmonary Hypertension-Specific Therapy for Systemic Sclerosis

The impact of therapy for SSc-PH has not been elucidated, due to the lack of randomized trials, disparate endpoints, and heterogeneous populations and therapies employed.[111] Intuitively, early diagnosis and treatment of SSc-PH may favorably influence outcomes.[17,120,174,176,185,186] However, pharmacological therapy for SSc-PH is less effective than in IPAH[1,112,120,145,184] and survival benefit has not yet been established in clinical trials.[111] High-dose calcium channel blockers (CCB) may be beneficial in small subset of patients with IPAH (< 10%),[187–189] but are rarely efficacious in SSc-PH.[111,170] CCB have no role to treat SSc-PH, but may have a role for selected SSc patients with digital ischemia.[112] Chronic anticoagulation with warfarin in patients with IPAH was associated with improved survival in two retrospective studies[190,191] and one uncontrolled, single-center prospective study.[188] However, warfarin was not related to survival in one study of SSc-PH[171] and expert opinion is divided on this issue.[192] We do not recommend anticoagulants in patients with SSc-PH in the absence of additional risk factors.

Given the poor prognosis of untreated SSc-PH, most patients are treated. Objective benefit is often difficult to ascertain. Because of ease of administration, oral agents (i.e., ET-1 receptor antagonists [ETRA][4,145,171,193–195] or phosphodiesterase inhibitors [PDE5-I][145,196]) have been the mainstay of therapy for SSc-PH.[5] However, a review of randomized, controlled trials showed no benefit in exercise capacity (assessed by 6MWD) with oral agents for SSc-PH.[145] Parenteral prostanoids are reserved for patients with NYHA class IV or functional class III patients failing oral agents.[1,111,197] An expert panel of the EUSTAR published recommendations for treatment of SSc (all organ systems).[198] With respect to PH, four recommendations were made: (1) bosentan should be "strongly considered" to treat SSc-PH; (2) sitaxentan "may also be considered;" (3) sildenafil should be "considered for the treatment of SSc-PH patients in whom bosentan has been ineffective or cannot be used for safety reasons;" and (4) "IV epoprostenol should be considered for the treatment of patients with severe SSc-PH."[198] These recommendations reflect expert opinion but have not been validated in randomized trials.[199] Clements et al reported 228 patients with SSc-PH and 279 patients with IPAH seen at 60 sites in the United States from 2005 to 2007.[200] Survival at 3 years was worse in the SSc-PH group (60%) as compared with IPAH (77%), $p < 0.0001$. PH-specific agents utilized between the two groups differed, that is, ETRA monotherapy (66% with SSc; 54% with IPAH, $p = 0.048$); combination of ERA plus PDE5-1 (25 vs. 12%, $p = 0.003$); parenteral prostenoid (19 vs. 38%, $p = 0.0006$). British investigators described 315 patients with isolated SSc-PH, of whom 90% were treated with PH-specific therapy (monotherapy in 62%; combination therapy in 28%).[5] Of those receiving monotherapy, treatment included: ETRA (68%); prostanoid (17%); and PDE5-I (15%).[5] Overall survival was improved compared with earlier *historical* studies,[172] but the impact of specific therapeutic agents could not be assessed. Similarly, in a cohort of 122 patients with SSc-PH in North America, only 51 (41.8%) were receiving PH-specific therapy.[6] Of these 51 patients, treatment options included bosentan in 36 (70.1%); epoprostenol in 5 (9.8%); other in 10 (19.8%). Mathai et al reported 59 SSc-PH patients (20 with concomitant ILD).[171] Most patients were treated with ETRA as initial therapy. Type of initial PH therapy and the use of warfarin were not related to survival. In a report from John Hopkins, 69 of 76 (90.8%) patients with SSc-PH were treated with PH-specific agents.[176] Initial treatment consisted of ETRA in 26 (37.7%); PDE5-I in 34 (49.1%); IV prostacyclin in 8 (11.6%); high-dose CCB in 1 (1.4%). At the end of follow-up, therapy included: ETRA alone, $n = 10$ (14.5%); PDE5-I alone, $n = 19$ (27.5%); prostanoids alone, $n = 5$ (7.2%); and combined therapy, $n = 35$ (50.7%). The impact of treatment could not be assessed. However, survival was no better in the later phases of the study. In 2006, the PHAROS Registry (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) was established to clarify the risk of PH among patients with SSc, elucidate the clinical course, and assess the impact of therapy.[185] Hinchliff et al described the first 237 patients enrolled, including 71 with PH confirmed by RHC and 166 with "pre-PH" (i.e., risk factors for developing PH).[185] Risk factors endorsed for inclusion as high risk included: $DL_{CO}$ < 55%; $FVC/DL_{CO}$ ratio > 1.6; RVSP > 35 mm Hg on DE; moderate to severe ILD on chest CT. Data are premature at this point, but this study hopefully will enhance our understanding of treatment effects. In the sections that follow, experience with each class of PAH-specific agents will be discussed.

## Prostanoids

Continuous infusional therapy with IV epoprostenol[201] or trepostinil (IV or subcutaneous)[202–204] has been shown to be efficacious in patients with PAH in large randomized double-blind placebo-controlled (RDBPC) trials. However, patients with CTD-PH were either excluded or represented a distinct minority of patients enrolled in those trials, so one must be cautious about extrapolating findings from those studies to SSc-PH. A few studies have focused on SSc-PH. In an open label, randomized, multicenter trial, 111 patients with SSc-PH were randomized to either IV epoprostenol or "conventional" (i.e., no PH-specific) therapy for 12 weeks.[1] Exercise capacity (6MWD) and hemodynamics improved in the epoprostenol-treated group, but there was no difference in survival (four deaths in the



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epoprostenol cohort; five deaths in the conventional group).[1] Oudiz et al reported a subset of 90 patients with CTD-PH enrolled in two RDBPC trials of subcutaneous trepostinil for PH.[197] At 3 months, small but statistically significant improvements in CI, PVR, dyspnea-fatigue scores, and 6MWD were noted compared with placebo. The net gain compared with placebo in 6MWD was 25 m ($p = 0.055$). A small open-label study of 16 patients (six had CTD-PH) treated with IV trepostinil noted slight, but statistically significant, improvements in exercise capacity and hemodynamics at 12 weeks.[205] The use of parenteral agents in patients with SSc can be logistically difficult, particularly given sclerodactyly, musculoskeletal impairments, and potential for site and blood stream infections.[206] Importantly, fatal pulmonary edema associated with epoprostenol has been described in SSc patients with PCH.[109,110]

Inhaled prostanoids (e.g., iloprost) have been associated with anecdotal successes in SSc-PH[207,208] but data are limited, and the long-term benefit of aerosolized agents in CTD-PH has not been demonstrated.

## ET-1 Receptor Antagonists

Bosentan, an oral ETRA, was shown to be effective in two RDBPC trials in patients with IPAH or SSc-PH.[209,210] The pivotal trial, termed Bostentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1), randomized 213 patients with PH (IPAH [$n = 150$] or CTD-PH [$n = 63$]) to bosentan or placebo for 12 weeks.[210] All patients were in WHO class III or class IV. Bosentan was superior to placebo in several measures including: 6MWD; WHO class; time to clinical worsening, and Borg dyspnea score.[210] A disproportionate number of patients had IPAH, and the number of patients with SSc-PH was limited ($n = 47$). An analysis of CTD-PH patients enrolled in randomized clinical trials noted a *trend* toward improvement in 6MWD and improved survival compared with *historical* cohorts.[211] Williams et al compared 45 SSc-PH patients treated with bosentan with 47 historical controls (27 received prostanoids).[178] The survival rates were 81 and 71%, respectively, for 1- and 2-year in bosentan-treated patients as compared with 68 and 47% in historical controls ($p = 0.016$). PVR was stable in bosentan-treated patients but increased in historical controls ($p < 0.06$). In contrast, in a study from Johns Hopkins, bosentan was less effective in SSc-PH compared with IPAH.[195] In that study, 17 SSc-PH patients and 19 IPAH patients were treated with first-line bosentan.[195] The 1- and 2-year survival rates were 87 and 79% with SSc-PH and 100 and 100% with IPAH, respectively; further, NYHA functional class did not improve in the SSc-PH cohort after a mean follow-up of 13 months.[195] Joglekar et al retrospectively assessed 23 SSc-PH patients treated with bosentan for at least 18 months.[194] At 3 months, WHO functional class improved in 57%; none worsened. However, after 9 months, WHO functional class tended to worsen. SPAP did not change with therapy. Humbert et al similarly noted that bosentan was less effective in SSc-PH compared with IPAH.[193] These studies do not negate a treatment effect in patients with SSc-PH, but suggest that any benefit may be small.

Mathai et al reported 59 patients with SSc-PH (20 had concomitant ILD), all of whom received PH-specific therapy.[171] Initial therapy included an ETRA in 71% (15/20 with ILD-associated PH and 27/39 with sole PH). Overall 20 patients were treated with a continuous IV or subcutaneous prostenoid. A second drug was added in 32 patients (54%). Total 35 patients (59%) received warfarin. No patient with lone PH received immunosuppressive therapy whereas 15 patients with ILD-associated PH received immunosuppressive agents. Impact of therapy (any agent) could not be ascertained.

Launay et al treated 49 consecutive SSc-PH patients with first-line bosentan; 27 had concomitant ILD.[4] During follow-up, prostanoids were added in 17 patients and sildenafil was added in 5 patients. Bosentan was discontinued in five patients due to elevated liver transaminases. RHC was performed in 40/44 patients at 4 months. At 4 months, NYHA class and PVR decreased without a significant change in mPAP or mRAP; whereas 6MWD did not change. At 1-year, 16/19 patients underwent RHC again; at this time point, CI, PVR, NYHA class, and 6MWD were not significantly different from pretreatment baseline. By multivariate analysis, baseline and 4-month NYHA functional class and 4-month CI were independent factors associated with survival. The 1-, 2-, and 3-year survival rates were 80, 56, and 51%, respectively. Overall 23 patients died (47%) after a mean follow-up of 23 months. Among the 23 deaths, 9 were on prostanoid + bosentan; 14 died while on bosentan monotherapy. Progressive right heart failure was the cause of death in 22/23. In the entire cohort, 13 patients had significant ILD (FVC < 70% predicted). By 18 months, 8 of 13 patients with ILD had died.

Ambrisentan, another ETRA, improved 6MWD at 12 weeks in a RDBPC trial of PH (both IPAH and SSc-PH).[212] However, the benefit was larger in patients with IPAH (50–60 m) compared with CTD-PH (15–23 m).[212] Sitaxentan is another ETRA that may be used to treat PH (IPAH or CTD-PH).[213–216] In addition to beneficial effects in PH, ETRA (particularly bosentan) may improve skin perfusion in hands and reduce the occurrence of new digital ulcerations in SSc.[217–220] Despite extensive clinical use of ETRA in SSc-PH, the benefit of these agents has not been well documented.

### Phosphodiesterase Type V Inhibitors

Both sildenafil and tadalafil has been used in CTD-PH, with clinical improvement in some studies. In the sentinel SUPER Sildenafil Use in Pulmonary Arterial Hypertension RDBPC trial, patients with PH (IPAH or associated) were randomized to one of three doses of sildenafil (20, 40, or 80 mg three times a day) or placebo.[221] The primary endpoint (6MWD at 12 wk) improved in all three sildenafil-treated cohorts compared with placebo.[221] Post hoc analysis of 84 patients with CTD (45% had SSc) from that study noted modest improvement in 6MWD, hemodynamics, and functional class after 12 weeks of therapy.[196] Changes in 6MWD were as follows:

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20 mg (+ 45 m); 40 mg (+ 36 m); 80 mg (+ 15 m); placebo (−13 m). NYHA functional class improved in 29 to 42% of patients receiving sildenafil compared with 5% in the placebo cohort. Another PDE5-I, tadalafil, was associated with clinical improvement in patients with PH (idiopathic or associated).[222] In the sentinel RDBPC trial, tadalafil (doses 2.5, 5, 10, or 40 mg daily for 16 wk) was compared with placebo in 405 patients with PH (either idiopathic or associated); 55% of patients were on bosentan at the time of enrollment.[222] Only the 40 mg dose achieved statistically significant improvements in 6MWD, time to clinical worsening, and quality of life. The mean placebo-adjusted change in 6MWD was 44 m among bosentan naive patients compared with 23 m in patients receiving bosentan. NYHA functional class did not change. Although some of the patients in that study had CTD, these patients were not analyzed separately. In summary, data regarding PDE5-I are sparse, but either sildenafil or tadalafil are well tolerated and may be used in patients with SSc-PH. Data regarding efficacy (short or long term) are not robust.

### Combination Therapy

Although, combination therapy may offer an advantage in selected patients,[222] survival benefit has yet not been established.[223] Mathai et al reported 82 patients treated with bosentan monotherapy for PH (IPAH or SSc-PH).[224] Both groups improved clinically with bosentan, but ultimately deteriorated (median time to failure 792 and 458 d, respectively). Sildenafil was added in 13 patients with IPAH and 12 patients with SSc-PAH. After addition of sildenafil, WHO functional class improved in 5 out of 13 with IPAH and in 2 out of 12 with SSc-PH. 6MWD improved by 47 m in IPAH, but fell by 7 m in the SSc-PH cohort. In the PACES trial, sildenafil (dose 80 mg three times a day) was added to IV epoprostenol in patients with idiopathic- or associated-PH (21% of these patients had CTD and 11% had SSc).[225] No subset analysis was provided, but improvement was mainly in patients with IPAH. These data cast doubt on the incremental benefit achieved with combination therapy in SSc-PH patients. Australian investigators reported 112 patients with PH of diverse etiologies (IPAH [51%]; SSc [26%]; and other [23%]) who were treated with a second agent after failing monotherapy (mean time of monotherapy 18.7 mo).[226] In the entire cohort, dual therapy improved 6MWD, DE, WHO class at 1 year. Survival rates on dual therapy at 1- and 2-years were 93 and 79% for IPAH patients as compared with 72 and 48% of SSc-PH. These data again suggest that the incremental benefit of combination therapy is less in SSc-PH patients as compared with IPAH.

### Anti-Inflammatory Therapies

Perivascular inflammatory infiltrates have been noted in some patients with CTD-PH.[107] Anecdotal responses to immunosuppressive agents have been cited in PH complicating SLE or other CTDs,[7] but SSc has usually been unresponsive to immunosuppressive therapy.[7] However, favorable responses to corticosteroids and CYC were cited among patients with SLE/SSc overlap and PH.[8]

### Future Therapies

Imitinib, an inhibitor of tyrosine kinase and PDGF is currently being investigated for the treatment of PH[227,228] and for the treatment of SSc-related ILD and skin disease.[111]

## Lung Transplantation for Connective Tissue Disease

Lung Transplantation (LT) for CTD has been done infrequently, as many medical centers consider CTD to be a contraindication to LT. Concern about gastroesophageal reflux, renal impairment, and extrapulmonary organ involvement are relative contraindications to LT. CTD accounted for 359 of 30,673 (1.2%) LT performed worldwide from January 1995 to June 2010.[229] LT may be an option for CTD patients with severe PH failing medical therapy.[230,231] One study from two medical centers in the United States assessed mortality rates post LT for patients with SSc ($n = 29$), idiopathic pulmonary fibrosis (IPF) ($n = 70$), and IPAH ($n = 38$).[231] Cumulative survival rates at 6 months were 69% for SSc, 80% for IPF, and 79% for IPAH (not statistically different). By 2 years, cumulative survival was approximately 64% for all the three groups. We reported 1-year survival rates among LT recipients with SSc (93.4%) or IPF (86.9%), respectively.[230] A review of the literature from 1986 to 2006 detected 54 SSc patients who had undergone LT.[232] Survival rates at 2- and 5-years were 72 and 52%, respectively, which are comparable to other diseases receiving LT.

## Other Connective Tissue Disorders

PAH is a rare complication of other CTD (principally MCTD, SLE, and overlap syndrome).[9–11,233] British investigators described a cohort of 484 patients with CTD-PH: SSc, $n = 315$ (74%); MCTD, $n = 36$ (8%); SLE, ($n = 35$, 8%); dermatomyositis/polymyositis (DM/PM), $n = 18$ (4%); RA, $n = 13$ (3%); undifferentiated CTD, $n = 9$ (2%); Sjogren syndrome, $n = 3$ (1%).[5] Most patients were treated with immunosuppressive therapy (IST). The survival rates of 1- and 3-year for isolated PH were as follows: SSc, 78 and 47%; SLE, 78 and 74%; DM/PM, 100 and 100%; MCTD, 89 and 63%; RA, 83 and 66%, respectively.[5] Korean investigators reported 20 SLE patients with PH and 34 patients with IPAH.[10] Survival rates at 3- and 5-years were 44.9 and 16.8% for SLE-PH as compared with 73.4 and 68.2% for IPAH ($p = 0.02$). Sanchez et al treated 28 patients with CTD-PH with IV pulse CYC; 22 received concomitant corticosteroids.[7] Five of 12 patients with SLE and 3 of 8 with MCTD responded (functionally and/or hemodynamically) without need for PH-specific therapy; all 7 patients with SSc were non-responders.[7] In another study, 7 of 8 patients with SLE-PH (4 had SSc overlap) responded to corticosteroids +/− CYC.[8] In a series of 23 patients with SLE or MCTD-associated PH, 16 were initially treated with immunosuppressive therapy alone, with 8 responders (50%).[234] Six of 8 non-responders improved with the addition of pulmonary vasodilators. Seven patients were *initially* treated with *both* immunosuppressive therapy and pulmonary vasodilators, with 4 responses (57%). PAH is a rare complication of Sjogren's



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syndrome.[235] The largest series comprised 28 patients (27 were females); survival rates were 73% at 1-year and 66% at 3-years. The impact of PAH-specific and immunosuppressive agents was modest. Although data are limited, early and aggressive therapy with immunosuppressive agents is recommended for CTD-PH in diseases other than SSc; PH-specific therapy may be efficacious for patients failing immunosuppressive therapy or with severe disease.

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