Pulmonary Hypertension Complicating Connective Tissue Disease

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Semin Respir Crit Care Med 2017;38:619–635.

Abstract

Pulmonary hypertension (PH) may complicate connective tissue disease (CTD; particularly systemic sclerosis [scleroderma]), and is associated with increased mortality. More than 70% of cases of PH complicating CTD occur in patients with systemic sclerosis (SSc), which is the major focus of this article. Pulmonary complications (i.e., interstitial lung disease [ILD] and PH) are the leading causes of SSc-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 in improving CTD-PH outcomes is under investigation, as prognosis and responsiveness to therapy appear to be 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 who fail medical therapy.

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

Pulmonary hypertension (PH) may complicate connective tissue disease (CTD), including systemic sclerosis (SSc),[1–6] systemic lupus erythematosus (SLE),[7–11] mixed connective tissue disease (MCTD),[5,6,8] and CTD overlap syndrome.[5,7,12] SSc accounts for the majority of cases of CTD-PH,[5] and is the major focus of this article. We reviewed this topic in a previous issue[13] of *Seminars* in 2013; this article provides additional data and publications since that review.

Systemic Sclerosis

SSc is a CTD characterized by inflammation, vasculopathy, and fibrosis, and may affect multiple organ systems (e.g., skin, lungs, gastrointestinal [GI] tract, kidney, heart).[14–18] PH occurs in 7.5 to 20% of patients with SSc[5,12,15,19–26] and is the second-leading cause of death in SSc.[27]

Broad Overview of Clinical Manifestations of Systemic Sclerosis

The diagnosis of SSc is based on the presence of a constellation of clinical signs and symptoms often found in the setting of specific autoantibody profiles. Dermatologic manifestations include cutaneous sclerosis, skin ulcers, digital pitting scars, telangiectasias, and calcinosis. Signs of internal organ dysfunction include upper and lower GI tract dysmotility, interstitial lung disease (ILD), PH, cardiac complications, and renal impairment. Raynaud's phenomenon is present in virtually all patients with SSc and can be present for several years prior to the onset of cutaneous sclerosis, particularly among patients with limited cutaneous sclerosis.[14,15,28]

The presence of distinct SSc-associated autoantibodies can predict the phenotypic expression of SSc and also provide important prognostic information[29–31] (discussed in detail later). Nailfold capillaroscopy can detect sclerodermatous

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Issue Theme Evolving Concepts in Pulmonary Hypertension; Guest Editor: Marc Humbert, MD, PhD

DOI https://doi.org/10.1055/s-0037-1606203.
ISSN 1069-3424.

microvascular changes, including capillary loss, distortion, hemorrhage, and dilatation, and some studies have found that these changes correlate with the extent of organ involvement.[32–34]

Classification of Systemic Sclerosis

The new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria[35] for SSc has improved sensitivity (91%) and specificity (92%) compared with the prior criteria proposed by the ACR in 1980.[16] In 1988, LeRoy et al classified SSc patients into limited and diffuse subsets based on the distribution of skin sclerosis,[15,17,34] and this distinction has important prognostic implications.[17] Patients with limited cutaneous systemic sclerosis (lcSSc) have cutaneous sclerosis of the distal extremities (i.e., forearms, hands, lower legs, feet, face), while patients with diffuse cutaneous systemic sclerosis (dcSSc) may have cutaneous sclerosis of the chest, abdomen, thighs, and upper arms, in addition to the areas affected in lcSSc.[15,17,25,34,36] Patients with both lcSSc and dcSSc can develop serious internal organ involvement, although the evolution of these complications typically occurs more rapidly in patients with dcSSc.[13,28,37] While isolated PH occurs more commonly in patients with lcSSc compared with dcSSC,[37,38] both subgroups can develop ILD. However, the risk of developing renal crisis is higher in dcSSc than in lcSSc patients, with an odds ratio (OR) of more than 7 in dcSSc patients.[39]

Rarely, SSc patients exhibit classic signs and symptoms of SSc *without* obvious cutaneous involvement (termed "sine scleroderma").[14,15,34,40] Historically, the acronym CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) syndrome was used to define a subset of patients with SSc,[41] but most consider this term to be obsolete.[14] Approximately 10% of SSc patients have signs of other defined CTDs, such as SLE, rheumatoid arthritis, and polymyositis (termed "overlap syndrome").[12]

Epidemiology of Systemic Sclerosis

The incidence of SSc ranges from 2.3 to 22.8 per million/year; the prevalence ranges from 88 to 280 per million.[14,15,42,43] The majority of patients with SSc are women (80%),[14,15,36,44] between the ages of 45 and 64 years.[15,36] Geographic variation in the prevalence of SSc exists.[42,43,45,46] 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.[42,47–49] The incidence is higher among blacks, but no other significant ethnic differences in distribution have been documented.[14,15,42,50]

Genetic factors may explain some of the geographic differences observed in the prevalence rates. Clusters of SSc cases exist within certain families, Choctaw Indians, as well as other ethnic groups.[14,42,51] Furthermore, genetic studies have identified SSc-associated polymorphisms of genes encoding cytokines, cytokine receptors, chemokines, and extracellular proteins.[14,51] While some studies have suggested that environmental factors (e.g., silica, solvents) may augment the risk of SSc, thus far, no single factor has emerged as universally causative factor.[52] One recent study found that SSc patients in France had higher median levels of heavy metals compared with controls.[53]

General Prognosis of Patients with Systemic Sclerosis

Organ Involvement in Systemic Sclerosis

SSc has the highest cause-specific mortality of all of the CTDs,[15,54,55] but the clinical expression and prognosis of SSc vary considerably.[14,15,17] While patients with dcSSc can more rapidly develop organ dysfunction compared with patients with lcSSc, involvement of visceral organs (principally lungs, kidneys, and heart) is the major factor determining prognosis.[14,15,37,44] The frequency of organ involvement varies across prior studies as criteria for specific organ involvement are not uniform within these studies.[15,37,56] Specific organ complications occurred at the following rates: kidney (19%), heart (15%), lung (16%), GI tract (8%), and skin (24%),[37] most of the severe complications occurring within 3 to 4 years of presentation.[37] In a systematic review of 69 SSc studies, the pooled prevalence of organ complications in dcSSc was approximately 15%, cardiac involvement (15%), PH by right heart catheterization (RHC) (15%), digital ulcers (15%), myositis (13%), inflammatory arthritis (12%), and renal crisis (15%).[26]

Presently, PH and ILD together account for 60% of SSc-related deaths.[27,44] Previously, renal crisis was the leading cause of death in SSc.[37] The incidence of renal-related deaths diminished dramatically following the introduction of angiotensin-converting enzyme (ACE) inhibitors in the 1980s among patients with renal crisis.[37,44,57] EULAR Scleroderma Trials and Research (EUSTAR) database (inaugurated in June 2004) prospectively followed 5,860 SSc patients from 151 centers for a mean of 0.9 years; during this time, 5.2% of patients died.[27] Among SSc-related deaths, attributable causes included ILD (35%), PH (26%), cardiac (26%), renal (4%), GI tract (3%).

Survival in Systemic Sclerosis

Reported SSc survival rates vary by country.[12,15,25,56,58–65] Differences between geographically distinct cohorts may be due to genetic factors, environmental factors, as well as differences in therapeutic approaches[25,56,66] (►**Table 1**).

Risk factors for mortality in SSc based on single-center studies include male gender;[14] lung, heart, or kidney involvement;[15,58,65] older age;[15,56,65] shorter duration of Raynaud's at the disease onset;[15] and greater extent of cutaneous sclerosis.[62] Factors associated with decreased mortality include the presence of the anticentromere antibody (ACA).[48] Specific laboratory tests are associated with increased mortality in SSc. The presence of anti-topoisomerase antibody,[15,48,58,59] U1 autoantibodies,[15,46] and RNA polymerase (RNAP) antibodies,[59] as well as an increased sedimentation rate ($\geq$ 25 mm/h),[56] and decreased hemoglobin $<$ 12.5 g/dL each independently predict mortality in SSc.

Table 1 Survival in systemic sclerosis varies across geographically distinct cohorts

Region	*N*	Survival
Italy[15]	1,012	10 y for patients recruited between 1955 and 1985: 60.6%
		10 y for patients recruited between 1986 and 1999: 76.8%
Japan[48]	496	5 y: 93.7%
		10 y: 82%
Canada[56]	309	5 y: 91.7% (lcSSc); 78.6% (dcSSc)
		10 y: 79% (lcSSc); 62.4% (dcSSc)
Sweden[67]	249	5 y: 86%
		10 y: 69%
Denmark[59]	174	13-y follow-up: 62.1%
Australia[64]	177	10 y: 71% (sclerodactyly only); 58% (cutaneous sclerosis proximal to the MCPs); 21% (dcSSc)
Spain[63]	79	15 y: 62%
Europe[27]	2,940	Mean 0.9-y follow-up: 94.8%
Netherlands[68]	460	15-y follow-up: 75.1% (lcSSc ATA positive); 57.9% (lcSSc ATA negative); 52.9% (dcSSc ATA positive)
Spain[69]	1326	5 y: 95.5%
		10 y: 91.2%
		20 y 79.2%
		30 y: 65.3%
Iran[70]	220	5 y: 92.6%
		10 y: 82.3%
Norway[71]	312	5 y: 98% (lcSSc); 91% (dcSSc)
		10 y: 93% (lcSSc); 70% (dcSSc)
Pennsylvania[44]	2,125	10 y: 54–66% (over a 30-y recruitment period)
Hungary[72]		5 y: 90.5% (lcSSc); 67% (dcSSc)
		10 y: 81.8% (lcSSc); 48.6% (dcSSc)

Abbreviations: ATA, anti-topoisomerase antibodies; dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; MCP, metacarpophalangeal.

An analysis of the EUSTAR database ($N = 5{,}860$ SSc patients) determined that independent predictors of mortality included proteinuria, PH; forced vital capacity (FVC) less than 80%, dyspnea on exertion, reduced diffusing capacity for carbon monoxide (DL_{CO}), older age at SSc onset, and severity of skin thickness.[27] Among patients with dcSSc, severe organ involvement occurs early in the course of the disease (first 3 years), and is associated with worse survival.[37] Furthermore, the greatest decline in FVC occurred during the first 2 years of the disease.[73]

Scleroderma Autoantibodies

The majority of patients (>95%) with SSc have a positive antinuclear antibody (ANA). More specific SSc autoantibodies include the ACA (present in 40–70%) and anti-topoisomerase-1 (also known as anti-Scl-70), found in 12 to 40%, but the prevalence of these autoantibodies in SSc varies widely.[14,15,22,29,40,56,66,74–76] Importantly, ACA and anti-topoisomerase-1 is almost always mutually exclusive.[15,29,30,74,77,78] Additional antinuclear antibodies have been detected in SSc patients,[15,29,30,79] including RNAP I, II, and III.[30] This is an evolving area of SSc research and the putative roles of existing and newly discovered autoantibodies in the pathogenesis of SSc are poorly understood.

Influence of the Presence of Autoantibody on Clinical Features and Prognosis

Certain autoantibodies are associated with specific SSc phenotypes.[15,29,31,74] For instance, ACAs are almost exclusively found in lcSSc (96%)[14] and are associated with calcinosis and telangiectasias. By contrast, anti-Scl-70 is more common in patients with dcSSc[14,73] and is associated with peripheral vascular disease (pitting scars) and more severe ILD.[15,29,62,75,79–81]

Anti-RNAP III is another important SSc-associated antibody and is found in 45% of patients with dcSSc, but in only 6% of lcSSc and 0% with CTD overlap syndrome.[82] SSc patients with anti-RNAP III had a significantly higher mean maximum skin thickness scores, but lower rates of telangiectasias, inflammatory myopathy, restrictive lung disease, or serious cardiac manifestations compared with SSc patients with anti-Scl-70.[82] While patients with anti-RNAP III typically have more extensive cutaneous sclerosis early in the disease course, dramatic improvements in (and in some cases complete resolution of) cutaneous sclerosis are often appreciated over a relatively short amount of time (i.e., 1–2 years).[83] Anti-RNAP III is also associated with a markedly increased risk for the development of renal crisis.[83]

Pulmonary Hypertension–Specific Autoantibodies

Certain autoantibodies occur more commonly in SSc patients with PH including ANA with a nucleolar pattern;[84] antifibrillarin antibodies (anti-U3-RNP);[85] fibrin-bound tissue plasminogen activator;[86] anti-topoisomerase II-α antibodies, particularly in association with HLA-B35 antigen;[87] antiendothelial cell IgG antibodies;[88,89] anti-Th/To;[90] and ACA.[29,75,79,90] Some evidence suggests that certain autoantibodies (e.g., anti-U1-RNP and anti-dsDNA) may promote an inflammatory pulmonary vasculopathy[91] and may contribute to the pathogenesis of vascular remodeling in PH.[92]

Pulmonary Hypertension in SSc

Pathology of SSc-PH

While the pulmonary arterial/arteriolar lesions observed in SSc-PH may be similar to idiopathic PAH (IPAH), pathological features unique to SSc include fibrous remodeling of the pulmonary venous system, with occlusive lesions in veins/

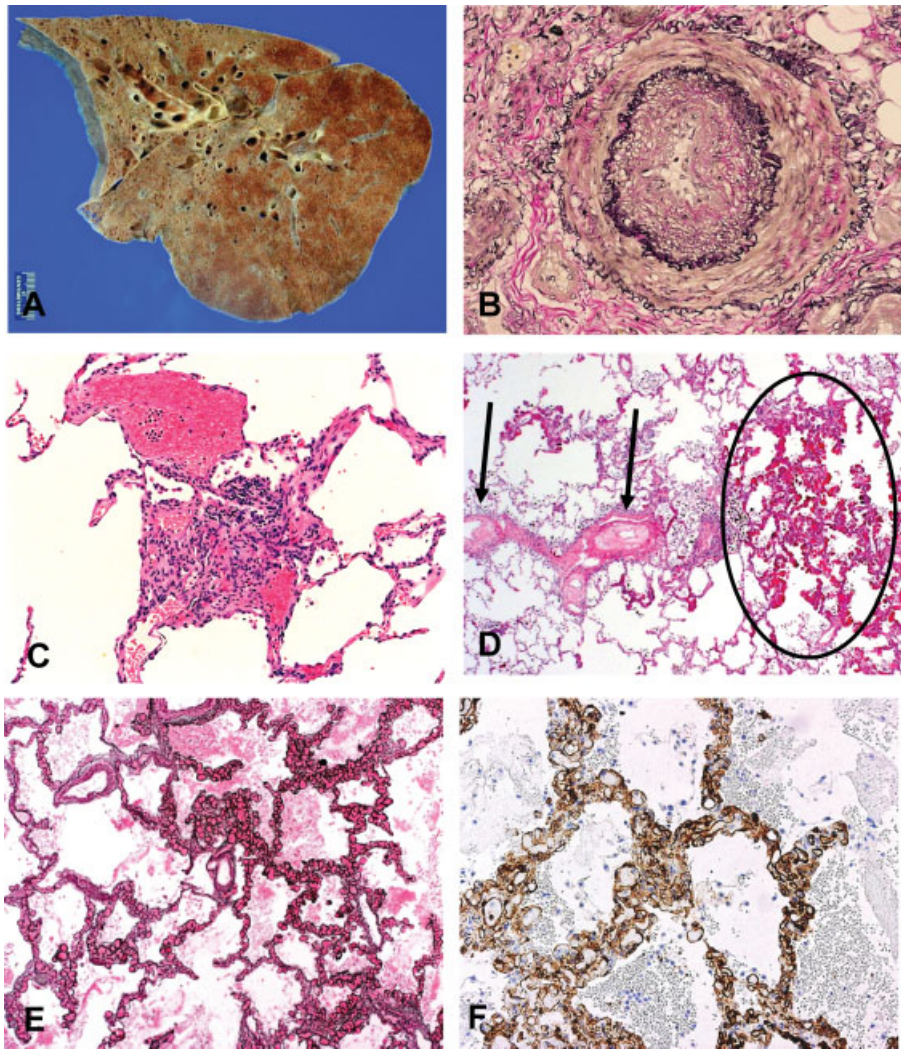

Fig. 1 Vascular changes in "scleroderma lung." (**A**) Gross lung with interstitial fibrosis in a UIP pattern; (**B**) typical arterial lesion with medial hypertrophy and intimal fibrosis (EVG stain, ×100); (**C**) plexiform/angiomatoid lesion that has been described in PSS but is rare in our experience (H&E stain ×100); (**D**) pulmonary venous occlusive disease (arrows) and pulmonary capillary hemangiomatosis (PCH; oval), often seen together when present in PSS (H&E, ×40); (**E**) PCH demonstrated by reticulin stain (×40), and (**F**) PCH demonstrated by CD34 immunohistochemistry (×100). PCH, pulmonarycapillary hemangiomatosis; UIP, usual interstitial pneumonia.

preseptal venules (resembling pulmonary venoocclusive disease [PVOD]), and capillary angioproliferation and postcapillary congestion[93,94] (►**Fig. 1A–F**). By contrast, plexogenic vasculopathy, which can occur in IPAH, has not been observed in SSc-PH.[93,94]

Pathogenesis of PH in SSc

Accumulating evidence suggests that specific components of the immune system may perpetuate inflammation in the pulmonary vasculature in SSc-PH, including T and B lymphocytes, macrophages, dendritic cells, and leukocytes. In addition to inflammation, vascular changes have been observed in SSc-PH, including endothelial cell (EC) activation, inflammatory cell recruitment, a procoagulant state,[95] endothelial injury,[96] and intimal proliferation and fibrosis leading to vessel obliteration.[96] Circulating vascular endothelial growth factors (VEGFs) may be increased in SSc,[97] and autoantibodies may also upregulate adhesion molecules,[91] leading to a proliferative vasculopathy.

Specific peripheral proteins are elevated among SSc-PH patients and may contribute to the pathogenesis of this condition. In one recent study, plasma sFlt-1 and placental growth factor (PlGF), regulators of angiogenesis, were higher in the 37 patients with SSc-PH than in 40 SSc patients who did not develop PH.[98] In a Norwegian study of 298 patients with SSc, circulating endostatin levels were higher in patients with SSc compared with normal controls,[99] confirming the results of an earlier smaller study.[100] Endostatin is the most potent inhibitor of VEGF-induced angiogenesis. Further, in a univariate logistic regression analysis, elevated endostatin predicted the onset of PAH within 2 years (OR was 1.7 (CI: 1.2–2.4, $p = 0.005$), whereas the multivariate analysis failed to confirm the predictive value of endostatin for the onset of PAH.[99]

Diagnosis of PH in SSc

Right Heart Catheterization

RHC remains the gold standard for the diagnosis of PH[101,102] and specific RHC findings have important prognostic implications.[103,104] Baseline resting hemodynamic data (particularly right atrial pressure [RAP], cardiac index [CI], and pulmonary vascular resistance [PVR]) predict disease severity and prognosis in IPAH,[103] but may be less predictive of clinical evolution of the disease in SSc-PH.[96,105]

Transthoracic Echocardiography

Transthoracic echocardiography (TTE) is often used as a screening technique for suspected PH[6,22,106] and also for monitoring the disease course and response to PH-specific therapy.[107] Signs associated with the presence of PH include elevated estimated right ventricular systolic pressure (RVSP), right ventricular (RV) dilation or dysfunction, and flattening of the interventricular septum.[101] However, assessment of RVSP requires adequate visualization of the tricuspid regurgitation jet, which is possible in less than 70% of cases.[101,108] Other parameters of interest in PH include the Tei index,[109] tricuspid annual peak systolic velocity,[110] and tricuspid annual plane systolic excursion (TAPSE).[111] While TTE may reliably predict the presence of severe PH, it is not a sensitive marker of mild to moderate PH.[22,107] The appropriate parameters and threshold ranges for the diagnosis (or exclusion) of PH have not been validated even though an RVSP $\geq$35 mm Hg is often used as a surrogate marker for PH.

In a prospective study of 137 patients with SSc (52 had concomitant ILD),[107] 99 (73%) had PH by RHC. In this study, the estimated tricuspid gradient (TG) by TTE showed a modest positive correlation ($r^2 = 0.44$, $p < 0.005$) with the mean pulmonary arterial pressure (mPAP) by RHC.[107] Applying a TG threshold of $\geq$45 mm Hg on TTE, the sensitivity and specificity for RHC-proven PH was 58 and 97%, respectively. Lower TG thresholds yielded higher false-positive rates. Taken together, these findings suggest that TTE is a reasonable, albeit imperfect, screening approach to identify SSc patients with PH. European guidelines suggest annual screening of SSc patients (even asymptomatic) for PH using TTE, but do not recommend screening for PH in patients with other CTDs unless symptoms suggestive of PH are present.[102]

Exercise TTE[112,113] may be useful for detecting early PH in SSc; however, no studies have provided substantial evidence that this is a valid screening approach for PH in SSc. Adding CT pulmonary angiography (CTPA) testing to TTE may improve the diagnostic accuracy over TTE alone.[114]

Pulmonary Function Tests

Pulmonary function test (PFT) parameters may be used to help predict the presence of PH, especially if they are serially measured. While a reduced DL_{CO} in the setting of low lung volumes suggests ILD, a DL_{CO} less than 65% predicted with normal or mildly reduced lung volumes or a decrease in the DL_{CO} $\geq$20% over 1 year suggests PH. The ratio of FVC to DL_{CO} can also predict PH. When this ratio is higher than 1.6, the likelihood of PH increases.[115]

Several formulas exist for predicting the presence of PH using PFT parameters.[116,117] These equations are typically created using a derivation cohort from a single center and validated using a separate cohort from the same center. For example, a study of 1,165 consecutive SSc patients in France developed a risk prediction score based on the following variables: age, FVC, and DL_{CO}/alveolar volume (V_A).[117] The validation cohort in this particular study consisted of 443 SSc patients *without* PH at baseline, 20 of who (4.5%) developed PH during a 3-year follow-up period.[117] In patients with low-risk scores, PH developed in only 0.6% of patients. Thus, this formula provides not only information about the presence of PH but also the likelihood of developing PH in the future among patients with SSc.

Elevated N-Terminus Pro-Brain Natriuretic Peptide

Elevated N-terminus pro-brain natriuretic peptide (NT-proBNP) concentrations predict PH, and serial measurements of NT-proBNP are often used clinically to monitor disease course and response to PH-targeted therapy. Patients with SSc-PH have elevated NT-proBNP levels compared with SSc patients without PH.[118,119] In a study of 109 patients with SSc (68 of who had PH documented by RHC), a NT-proBNP level of 395 pg/mL predicted PH, with a sensitivity of 56% and specificity of 95%.[118] Moreover, baseline NT-proBNP levels correlated with surrogate measures of PH severity, including the mPAP and PVR,[118] and also predicted mortality.[118,119]

DETECT Algorithm

The NT-proBNP level is a component of the recently developed DETECT algorithm for predicting PH in SSc. A prospective, international, multicenter study examined 466 patients with SSc deemed to be at risk for PAH (i.e., SSc duration >3 years, DL_{CO} <60% predicted).[120] All patients underwent RHC, and a PH-prediction algorithm was generated. The other components of the algorithm include FVC% predicted/DLCO% predicted, the presence of telangiectasias, the presence of ACA, serum urate level, and the presence of right axis deviation on electrocardiography (ECG). The false-negative rate using the algorithm was low (4%). The reliability of the DETECT algorithm has been confirmed in subsequent studies.[121]

Epidemiology of SSc-PH

Isolated PH complicates 5 to 20% of cases of SSc.[3,19–24,96,122] PH can also occur in conjunction with ILD and this is deemed "secondary" PH.[5,15,22,73] The prevalence per million in the United Kingdom in 2006 was 4.23 for CTD-PH and 2.93 for SSc-PH.[5] The incidence of PH among SSc patients in France over a 3-year period was 0.61 cases per 100 patient-years (patients with severe restrictive lung disease or left heart disease were excluded).[22]

However, the precise incidence and prevalence of PH in SSc is not entirely clear as varying diagnostic criteria have been applied in these studies. Some studies have used TTE to diagnose PH in SSc patients and have cited prevalence rates more than 30%.[123,124] Most studies cite prevalence rates of PH (by TTE) among SSc patients of 9.9 to 26.7%.[3,6,19,24,122,125,126]

Prevalence rates are generally lower when RHC is required to diagnose PH.[19–21]

Risk Factors for PH in SSc

Several factors may independently portend an increased risk of PH in patients with SSc,[18] including lcSSc;[96,126–128] disease duration >10 years;[96,129] late age of onset of SSc;[126,130] increased severity[131] or duration[128] of Raynaud's phenomenon; reduced nailfold capillary density;[129,132] a low (<70% predicted) or progressive decline in DL_{CO};[126,131,133] a DL_{CO} that is disproportionately decreased relative to the FVC (FVC% predicted to DLCO% predicted ratio >1.6);[134] and a DL_{CO}/VA ratio less than 70% or less than 60%.[135] Specific autoantibodies (e.g., anti-U3-RNP,[38,85] nucleolar pattern ANA, and ACA[29,75,79]) are associated with a higher incidence of PH. Also, exercise-induced PH on RHC and stress echocardiogram may be associated with an increased risk of PH in SSc.[5] Moreover, a borderline PAP (defined as mPAP 21–24) on RHC may be a risk factor for decreased exercise capacity and the future development of PH.[136]

The PHAROS Registry (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) is a U.S.-based registry established in 2006 to follow the course of PH in patients with SSc, and one of its aims is to examine SSc patients at risk for developing PH.[137] In their cohort of 251 patients with SSc at increased risk for PH (as defined by either a low DLCO [<55%] without ILD, a high FVC/DLCO ratio [>1.6], or systolic pulmonary arterial pressure (sPAP) >40 mm Hg on TTE), exercise-induced hypoxia, 6-minute walk distance (6MWD), and mean echocardiogram systolic PA pressure were significant risk factors for the future development of PH.[138] The average entry 6MWD for the patients who developed new PH was 353 m, versus 422 m for the patients who did not develop PH ($p = 0.038$).[138] The percentage of patients who had exercise-induced hypoxia who went on to develop PH was 54 versus 23% for patients who did not ($p = 0.003$). The mean sPAP for patients who eventually developed new PH was 43 mm Hg, versus 39 for those who did not.[138]

Prognosis of SSc-PH

The presence of isolated PH adversely affects survival in SSc (3-year survival approximating 50%),[2,5,96,118,122,139,140] and the prognosis is worse when ILD is also present.[3,5,96,141,142] Response to PH-specific therapy in SSc is generally poor[5,96,143] and the high mortality rate associated with PH in SSc may also be due to the concurrent presence of cardiac and pulmonary parenchymal involvement.[96,105]

The Registry to EValuate Early And Long-term PAH disease management (REVEAL), initiated in 2006, prospectively followed the course of patients in 54 U.S. pulmonary hypertension centers with WHO Group I Pulmonary Hypertension, and has 3,515 patients in the registry.[144] The prognosis for patients with SSc-PH is worse than patients with PH secondary to non-SSc autoimmune disease, as well as patients with IPAH.[144] In 2010, the REVEAL investigators reported that 1-year survival was 86% in the CTD-PH group compared with 93% in IPAH ($p < 0.0001$).[145] One-year survival was worse in SSc-PH (82%) compared with other CTD-PH diagnoses (SLE [94%], MCTD [88%], RA [96%]).[145] A follow-up publication of the REVEAL registry data in 2014 showed that 3-year survival rates for patients with newly diagnosed SSc-PH was 51%.[146] In comparison, the 3-year survival for all patients with PAH in the REVEAL registry was 68%, and the 3-year survival for patients with IPAH or familial PAH was 74%.[147] Meanwhile, the 3-year survival for patients with PH secondary to an autoimmune disease *other than SSc* was 76%.[146]

Another U.S.-based registry, with 791 patients, is the PAH Quality Enhancement Research Initiative (PAH-QuERI).[148] This registry cited 3-year survival of 60% in the SSc-PH group (60%) compared with 77% in the IPAH cohort ($p < 0.0001$).[148]

In the EUSTAR registry, which defines PH as an elevated estimated sPAP by TTE, the incidence of SSc-PH was 21%.[149] Only 16% (44 of 261) patients in the EUSTAR population with elevated sPAP by TTE went on to have a RHC performed.[150] The hazard ratio for sPAP as a risk factor for death, regardless of whether a RHC was performed, was 3.02, and the estimated 5-year survival was 57% in patients with sPAP greater than 35 mm Hg and just 28% in patients with sPAP greater than 50.[150]

Previous studies examined survival rates of subgroups of patients with SSc-PH. British investigators followed 315 new incident cases of SSc-PH (confirmed by RHC) for a mean of 3.3 years.[5] One- and 3-year survival rates for "isolated" SSc-PH were 78 and 47%, respectively. However, among SSc patients with PH and ILD, the 3-year survival was only 28% ($p = 0.005$). Younger age, female sex, higher mixed venous oxygen saturation (Sv02), and lower World Health Organization (WHO) functional class were independent predictors of survival.[5] Survival rates from another UK study of 89 patients with SSc-PH (confirmed by RHC) reported survival rates at 1, 2, and 3 years of 81, 63, and 56%, respectively.[19]

A cohort of 91 consecutive patients from Johns Hopkins University (SSc-PH [$n = 50$]; IPAH [$n = 41$]) reported 1- and 3-year survival rates of 88 and 49%, respectively, in SSc-PH patients compared with 95 and 84%, respectively, in IPAH.[105] Overall, mortality was higher in patients with SSc-PH even though the mPAP was lower in the SSc patients (46.6 mm Hg) compared with IPAH (54.4 mm Hg).[105] In this study[105] and other studies,[63,139,151] the presence of a pericardial effusion predicted poor outcomes. Pericardial effusion may occur as a result of increased right heart pressure[152] or the presence of serositis.[151]

Additional factors which portend a poor prognosis in SSc-PH include male sex,[5] late age at diagnosis,[5] hyponatremia,[153] advanced WHO functional class,[5,154] reduced DL_{CO},[141] reduced 6-MWD,[19,154] elevated BNP,[118] impaired renal function,[155] concomitant ILD,[3,5,96,141] pericardial effusion,[105] low stroke volume,[155,156] and cardiac disease.[96] Intrinsic cardiac disease in SSc may impair RV contractility and the ability of the RV to adapt to pressure overload.[157] One study found that SSc-PH patients exhibited lower stroke volumes for any given mean RV pressure compared with IPAH patients.[158]

Another important prognostic factor in SSc-PH is the present of ILD.[3–5,19,141,159] Among a cohort of 59 SSc patients with PH (20 had concomitant ILD), 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).[141] These findings are consistent with those reported by Launay and colleagues, in which the 3-year survival rates were lower in SSc-PH-ILD (47%; $n = 47$) compared with SSc-PH (71%; $n = 50$).[159]

In the setting of ILD, the use of PH therapy in SSc remains controversial. While data assessing the efficacy of PH therapy in patients with SSc-PH-ILD are scarce,[96,141,160] one retrospective study found that initiation of PH therapy in 70 patients with SSc-PH-ILD did not change 6MWD, WHO class, or hemodynamics with therapy.[161] Survival at 1, 2, and 3 years were 71, 39, and 29%, respectively.[161] Another retrospective study found that early initiation of prostacyclin therapy (within 6 months of the diagnostic RHC) was associated with improved survival in patients with SSc-PH ($N = 99$), among whom 72% had SSc-PH-ILD.[142] Clearly, more prospective studies are needed to determine whether PH therapy improves prognosis in the setting of ILD in patients with SSc.

PH-Specific Therapy for SSc

The most prominent society treatment guidelines for the management of PH include those of the World Symposium on Pulmonary Hypertension (WSPH), which convened in 2013 in Nice, France.[162] In addition, the joint guidelines of the European Society of Cardiology (ESC) and European Respiratory Society (ERS) were last updated in 2015,[163] and the American College of Chest Physicians (ACCP) guidelines were updated in 2014.[164] Due to the relative lack of randomized trials, in conjunction with retrospective studies with heterogeneous endpoints, study populations, follow-up periods, and therapeutic interventions, the efficacy and safety of therapies specifically for SSc-PH is poorly understood. Therefore, the aforementioned guidelines differ in their recommendations regarding the management of SSc-PH. For example, the ESC/ERS and WSPH guidelines state that high-quality data support the use of epoprostenol in SSc-PH, while the ACCP guidelines do not specifically address SSc-PH.

Theoretically, early diagnosis and treatment of SSc-PH may improve health outcomes.[18,137,155,165–167] However, pharmacological therapy for SSc-PH is less effective than for IPAH[1,143,161,165,168] and clinical trials have not yet demonstrated a survival benefit in SSc-PH;[96] however, REVEAL registry data suggested that SSc-PH patients are offered significantly less combination and prostacyclin-based PH therapies compared with IPAH.[145] Oral agents (i.e., ET-1 receptor antagonists [ETRA][4,141,168–171] or phosphodiesterase inhibitors [PDE5-I])[168,172] are often first-line therapy for SSc-PH.[5] However, a review of randomized clinical trials (RCTs) demonstrated that these oral agents do not improve exercise capacity (assessed by 6MWD) in SSc-PH.[168] 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%), and other in 10 (19.8%). Mathai et al reported 59 SSc-PH patients (20 with concomitant ILD),[141] the majority of whom were treated with ETRA as initial therapy. Type of initial PH therapy and the use of warfarin did not affect survival. Below, we review data for each of the agents currently used for SSc-PH.

Prostanoids

Parenteral prostanoids are reserved for PH patients with New York Heart Association (NYHA) class IV or functional class III patients failing oral agents.[1,96,173] Continuous therapy with intravenous (IV) epoprostenol[174] or treprostinil (IV or subcutaneous)[175–177] is effective in patients with IPAH based on RCT, but few CTD-PH patients were enrolled in those studies.

One randomized, open-label study assessed the efficacy of IV epoprostenol (compared with non–PH-specific therapy) in 111 SSc patients with moderate to severe PAH over 12 weeks.[1] Exercise capacity (based on 6MWD) and hemodynamics improved in the epoprostenol-treated group, but there was no difference in survival (four deaths in the epoprostenol cohort; five deaths in the conventional group).[1] Importantly, this study was not statistically powered to evaluate the effect of epoprostenol on mortality. In another study of 90 patients with CTD-PH, treatment with subcutaneous treprostinil for 3 months resulted in small, but statistically significant improvements in CI, PVR, dyspnea-fatigue scores, and 6MWD compared with placebo.[173]

The use of parenteral agents in patients with SSc may be limited secondary to access issues in the setting of severe cutaneous sclerosis and/or joint contractures. Complications of parenteral administration of prostacyclins include bloodstream infections,[178] as well as fatal pulmonary edema, which has been observed in SSc patients with the pulmonary capillary hemangiomatosis (PCH) and PVOD spectrum of disease.[179,180] Inhaled prostanoids (e.g., iloprost) are rarely used in SSc-PH, as there is minimal evidence supporting their efficacy.[181,182]

Treprostinil is now available in oral formulation, which potentially obviates the above concerns with employing infusional devices in patients with cutaneous sclerosis,[178] and the medication has FDA approval for use in all group I PAH patients including those with SSc-PH. However, the data for oral treprostinil are not as robust as the data for subcutaneous and IV infusion. Two studies investigating the effect of adding treprostinil to background therapy of ERA, PDE5 inhibitor, or combination failed to show a statistically significant improvement in the primary endpoint of improvement in 6MWD.[183,184] About 30% of the study population had CTD-PH, and they fared even worse than the IPAH cohort, with a nonstatistically significant *decrease* in mean walk distance for CTD-PH patients taking study drug (−4.0 m; 95% CI, −25 to 20 m), compared with the trend toward increase in IPAH patients (14.0 m, 95% CI, 0–28 m).[183]

ET-1 Receptor Antagonists

Two RCTs have demonstrated the efficacy of bosentan, an oral ETRA, for patients with IPAH and SSc-PH.[185,186] The Bostentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) randomized 213 patients with PH

(IPAH [$n = 150$], SSc-PH [$n = 47$], non-SSc CTD-PH [$n = 16$], all WHO class III or IV) to bosentan versus placebo for 12 weeks.[186] A significant treatment effect was observed for the following endpoints: 6MWD, improvement in WHO class, time to clinical worsening (TTCW), and Borg dyspnea score.[186] Denton and colleagues[187] performed an in-depth analysis of the CTD-PH enrolled in the aforementioned RCTs[185,186] and failed to demonstrate a statistically significant improvement in 6MWD, though they reported a trend in favor of bosentan, with the mean 6MWD 22.1 m higher in the bosentan group, but a 95% CI ranging from −32 to 76 m.[187] Additional studies have compared CTD-PH patients treated with bosentan in RCTs and compared these patients with untreated historical controls.[154,187] These studies have demonstrated favorable treatment effects on 6MWD,[187] PVR,[154] and survival.[154] However, the results should be interpreted with caution because the use of a historical control cohort can lead to systematic bias and confounding.

A RCT demonstrated that ambrisentan, another ETRA, improved 6MWD at 12 weeks in patients with IPAH and SSc-PH.[188] However, similar to bosentan,[171] the improvement in 6MWD was greater in patients with IPAH (50–60 m) compared with CTD-PH (15–23 m).[188] Macitentan is the latest ETRA to gain approval for use in PH. In the sentinel study, 742 patients with PH (224 had CTD),[189] two different doses of macitentan were compared versus placebo. While treatment with macitentan reduced the risk of worsening of PH, no survival benefit was observed in the treatment arm.[189] Though this study did not focus specifically on patients with CTD-PH, a subgroup analysis of the patients with CTD-PH demonstrated no significant difference in the rate of meeting the primary outcome of complication of PH or death between macitentan versus placebo.[189] In addition to improving PH-related outcomes, ETRA may improve skin perfusion in hands[190] and reduce the occurrence of new digital ulcerations in SSc.[191–193]

Phosphodiesterase Type V Inhibitors

Sildenafil is also used to manage CTD-PH. In the SUPER-1 RCT, patients with PH (IPAH and CTD-PH) who were treated with varying dosages of sildenafil (20 mg, 40 mg, or 80 mg tid) had a significant improvement in 6MWD at 12 weeks compared with placebo.[194] A post hoc analysis of the 84 patients with CTD-PH in this study (45% had SSc) found modest improvement in 6MWD, hemodynamics, and functional class after 12 weeks of therapy.[172] Moreover, NYHA functional class improved in 29 to 42% of patients receiving sildenafil compared with 5% in the placebo cohort.

In a RCT of 405 patients with PH (IPAH and CTD-PH), treatment with tadalafil (doses 2.5, 5, 10, or 40 mg daily for 16 weeks) was associated with a significant improvement in 6MWD, TTCW, and quality of life, but only among the patients who received dosages of 40 mg daily.[195] Notably, 55% of patients in this study were on bosentan at the time of enrollment and the mean placebo-adjusted change in 6MWD was 44 m among bosentan-naive patients compared with 23 m in patients receiving bosentan. This study did not examine the CTD-PH patients separately.

Combination Vasodilator Therapy

Combination therapy is now frequently employed as a management strategy in CTD-PH.[195] In one study, sildenafil was added in 13 patients with IPAH and 12 patients with SSc-PAH who were initially treated with bosentan monotherapy.[196] After the addition of sildenafil, WHO functional class improved in 5 of 13 with IPAH and in only 2 of 12 with SSc-PH. The 6MWD improved on average by 47 m in IPAH, but declined by 7 m in the SSc-PH cohort. Sildenafil has also been added onto therapy with IV epoprostenol in patients with IPAH and CTD-PH (21% of all patients had non-SSc CTD and 11% had SSc).[197] Improvement occurred mainly in patients with IPAH in this study. Another study of 112 patients with PH of diverse etiologies (IPAH [51%], SSc [26%], other [23%]) found that adding a second agent in patients failing monotherapy (mean time of monotherapy: 18.7 months) led to improvements in 6MWD, TTE parameters, and WHO class at 1 year.[198] Survival rates on combination therapy were better among IPAH patients compared with SSc-PH patients (1- and 2-year survival rates were 93 and 79%, respectively, for IPAH patients compared with 72 and 48%, respectively, for SSc-PH).[198]

Clements et al examined 228 patients with SSc-PH and 279 patients with IPAH seen at 60 sites in the United States from 2005 to 2007.[148] PH-specific agents used between the two groups differed by the following (SSc vs. IPAH): ERA monotherapy (66 vs. 54%), combination of ERA plus PDE5-I (25 vs. 12%), and parenteral prostanoid (19 vs. 38%). 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 prior studies,[199] but the impact of specific therapeutic agents could not be assessed. In a report from John Hopkins, 69 of 76 (90.8%) patients with SSc-PH were treated with PH-specific agents.[155] Initial treatment consisted of ETRA in 26 (37.7%), PDE5-I in 34 (49.1%), IV prostacyclin in 8 (11.6%), and high-dose calcium channel blockers (CCBs) 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 2016, the PHAROS investigators published data comparing the efficacy of therapies on patients with SSc-PH confirmed by RHC. They used a composite primary outcome (TTCW), which consisted of the following variables: onset of death, PH-related hospitalization, lung transplantation (LT), initiation of parenteral prostanoid therapy, or worsening of symptoms. The group of patients taking ETRA alone were less likely to remain clinically stable: 34.8% were clinically stable at 3 years, compared with 68.2% in the combined ETRA/PDE5 inhibitor group and 80.8% in the PDE5-only group. Furthermore, 10 (41.6%) patients in the ETRA-only group died, compared with 1 (6.7%) in the combined therapy group, and 4 (6.8%) in the PDE5 inhibitor-only group.[200]

The PHAROS data supporting the use of combination therapy over ETRA alone is corroborated in the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) study, a RCT comparing tadalafil monotherapy, ambrisentan monotherapy, and tadalafil/ambrisentan combination therapy.[196] The study enrolled 610 patients, 187 of who had CTD-PH. The risk of clinical failure was lowest with combination therapy (18%), compared with the ambrisentan alone (34%) or tadalafil alone (28%).[196] The authors of AMBITION study did not publish subset analysis specifically regarding patients with CTD-PH, but this combination was studied in SSc-PH patients in a smaller trial out of Johns Hopkins.[201] Twenty-four patients with SSc-PH were treated with combination of ambrisentan and tadalafil, and the authors reported an improvement of 14% in the first primary outcome of RV mass as measured by cardiac magnetic resonance imaging (MRI), a decrease from 6.9 to 3.1 Wood units in PVR as the second primary outcome, and an improvement in mean 6MWD to 395 m from 343 m, which was a secondary outcome.[201] This study did not have a placebo control group.

Anticoagulation

Systemic anticoagulation with warfarin for PAH was previously included in the treatment algorithm for PAH at the fourth WSPH at Dana Point, California, in 2008, based on data from observational studies.[202] However, these studies occurred between 1984[203] and 1997,[204] prior to the availability of many current treatment modalities. Furthermore, a systematic review published in 2006 demonstrated that among seven studies examining survival in relation to anticoagulation use two of these studies did not support the use of anticoagulation.[205] Due to the lack of RCTs and the mixed results of the observational studies, anticoagulation for PAH has largely fallen out of favor and neither a recommendation for or against warfarin was listed in the treatment algorithm of the fifth World Symposium at Nice, France.[162] Recent studies have supported this shift, especially in the setting of SSc-PH. The Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry, a multinational European registry composed of 41 PH centers, found that among the 208 patients with SSc-PH, there was no improvement in mortality for the 104 patients treated with anticoagulation,[206] despite a mortality benefit for IPAH patients taking anticoagulation.[206]

Analysis of the REVEAL registry demonstrated that patients with SSc-PH who initiated warfarin after enrollment into the study had a significantly lower survival compared with matched controls; however, this survival difference was no longer significant once the analysis adjusted for baseline disease severity measures.[146] Taken together, the findings from these two large registry studies do not support the use of anticoagulation in CTD-PH.

Recently Approved Therapies

Riociguat, a stimulator of soluble guanylate cyclase, received FDA approval for use in patients with WHO group 1 PAH in 2013. In the sentinel article regarding riociguat, improvement in exercise capacity was noted among patients taking the study drug,[207] but the authors did not detail how the patients with CTD-PH fared. Instead, the study group published the data regarding the CTD-PH subgroup in 2017, showing a trend toward significance but not a statistically significant improvement in the primary outcome of improvement in exercise capacity both for CTD-PH patients as a group, or those with SSc-PH.[208] The authors commented that this finding was in line with prior studies that had showed less benefit among patients with CTD-PH compared with IPAH.[208]

Selexipag, an agonist of prostacyclin receptor, was approved by the FDA for use in patients in PAH, including patients with SSc-PH, in 2015. Selexipag monotherapy reduced the onset of a composite endpoint of death or complications of PH when compared with placebo.[209] The largest difference in complication rate was for disease progression (17.2% for the placebo arm vs. 6.6% for the treatment arm), and there was no mortality benefit. While this study included patients with CTD (29%; 334 of 1,156), no CTD subgroup analysis was performed. Nonetheless, like riociguat, selexipag is approved for use in all patients with WHO group I PAH, including those with SSc-PH.[210]

Experimental and Future Therapies

Case studies provided some early evidence that imatinib, an inhibitor of tyrosine kinase and platelet-derived growth factor (PDGF), may play a role in the treatment of CTD-PH.[211,212] However, a RCT of imatinib as add-on therapy demonstrated that PH patients randomized to imatinib had increased serious adverse events and drug discontinuations compared with placebo.[213]

Bardoxolone methyl is a suppressor of NF-κB and is currently under investigation for the treatment of PAH, including those with PAH associated with systemic inflammatory disease.[214] Beraprost-314d is an orally active prostacyclin analog with early positive results, and is currently being investigated in conjunction with inhaled treprostinil for patient with PAH, including CTD-PH[215] (NCT01908699).

Lung Transplantation for CTD

A growing number of LT procedures are being performed in patients with CTD who are failing PH medical therapy.[216,217] Historically, patients with CTD were precluded from LT due to concerns about gastroesophageal reflux (particularly in the setting of SSc) and extrapulmonary involvement characteristic of most CTDs. From 1995 to 2010, of 30,673 (1.2%) LTs performed worldwide 359 LTs were performed on patients with an underlying CTD.[218] In a two-center study, survival rates post-LT were similar at 6 months for patients with SSc ($n = 29$), idiopathic pulmonary fibrosis (IPF) ($n = 70$), and IPAH ($n = 38$).[217] By 2 years, cumulative survival was approximately 64% for all three groups. Our center previously reported improved 1-year survival rates among LT recipients with SSc (93.4%) compared with IPF (86.9%).[216] A review of 54 LTs in SSc from 1986 to 2006 reported survival rates at 2 and 5 years of 72 and 52%, respectively, which are comparable to other diseases receiving LT.[219]

More recent studies have not found any difference in post-LT survival between SSc patients and non-SSc patients with fibrotic lung diseases.[42,220–223] Furthermore, contrary to previous thought, severity of esophageal dysfunction by either morphometry or manometry criteria was not associated with survival in SSc-ILD patients ($n = 35$) who underwent LT at our center.[223] These findings are consistent with a prior single-center study, which found no association with the presence of esophageal dysfunction and survival.[221] Based on the aforementioned evidence, SSc should not be considered a contraindication to LT.

Other Connective Tissue Disorders

Compared with SSc, PAH occurs less often in the setting of other CTDs (principally MCTD, SLE, and CTD overlap syndromes).[9–11,224] British investigators described a cohort of 484 patients with CTD-PH and noted the following prevalences: SSc, $n = 315$ (74%); MCTD, $n = 36$ (8%); SLE, ($n = 35$, 8%); dermatomyositis/polymyositis (DM/PM), $n = 18$ (4%); rheumatoid arthritis (RA), $n = 13$ (3%); undifferentiated CTD, $n = 9$ (2%); and Sjögren's syndrome, $n = 3$ (1%).[5] Most patients were treated with immunosuppressive therapy (IST). One- and 3-year survival rates for isolated PH were as follows: SSc, 78 and 47%; SLE, 78 and 74%; DM/PM, 100 and 100%; MCTD, 89 and 63%; and RA, 83 and 66%, respectively.[5]

Systemic Lupus Erythematosus

The prevalence of SLE-PH ranges from 0.5 to 17.5%.[225] A French registry found that among 674 cases of PAH, 101 had CTD and 15 had SLE.[226,227] In the REVEAL Registry composed of 54 U.S. centers, 110 (out of 2,967 cases of PAH) had SLE-PAH.[145] One-year survival in this registry was significantly improved among SLE-PAH patients (92%) compared with patients with SSc-PAH (82%). A study from the United Kingdom reported a 3-year survival of 75% for patients with SLE-PAH versus 47% for patients with SSc-PAH.[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%, respectively, for SLE-PH compared with 73.4 and 68.2%, respectively, for IPAH ($p = 0.02$). In a Chinese registry of 1,934 patients with SLE, 3.8% had PAH,[228] and the SLE-PAH patients had significantly higher disease activity compared with SLE patients without PAH. In this cohort, the independent predictors of PAH were pericarditis, pleuritis, and anti-RNP antibody presence.[228]

While PH may develop anytime during the course of SLE, most often PH manifests within the first 5 years from the time of initial diagnosis.[229] PAH is the most common cause of PH in SLE, although all PH subgroups can occur in this condition. The presence of antiphospholipid antibodies,[230,231] anti-U1RNP antibody,[232] and possibly the lupus anticoagulant[233] may predict the presence of PAH in SLE.

Management strategies for SLE-PH are mostly based on outcomes from therapeutic trials for IPAH and CTD-PH. However, vasoactive therapy appears to be beneficial for SLE-PH. For example, a post hoc analysis of a trial comparing sildenafil with placebo for CTD-PH demonstrated that patients with SLE-PH treated with sildenafil ($n = 6$) had improved 6MWD and improved NYHA functional class compared with those treated with placebo ($n = 4$).[172] Another study of 12 SLE-PH patients found that treatment with PH-specific therapy for 3 months (i.e., epoprostenol [$n = 8$], bosentan [$n = 2$], or treprostinil [$n = 2$]) led to significant improvements in 6MWD and NYHA functional class, as well as significant decreases in mPAP and RVSP.[234]

In addition to vasodilator therapy, there is also some evidence that treatment with immunosuppression in conjunction with vasodilator therapy may improve outcomes in patients with SLE-PH.[235,236] A randomized controlled trial comparing monthly IV CYC for 6 months and daily oral enalapril in SLE-PAH patients ($n = 34$) demonstrated a favorable CYC-treatment effect on reducing the sPAP and NYHA functional class.[237] In a relatively large study of CTD-PH patients, treatment with aggressive immunosuppression in combination with vasodilator therapy improved hemodynamics and outcomes in six out of seven SLE patients.[5] While more SLE-PH trials are needed to further evaluate treatment strategies for this condition, the aforementioned findings suggest that aggressive treatment with vasodilator therapy and possibly immunosuppression may improve outcomes for patients with SLE-PH.

Mixed Connective Tissue Disease

PH can complicate MCTD, an anti-U1-RNP autoantibody-associated disease with features of SSc, SLE, and polymyositis. While the exact prevalence of PH in the setting of MCTD has not been well established, recent studies suggest that the prevalence may be lower than previously reported.[238] In a Norwegian multicenter cohort study of 147 unselected patients with MCTD followed up for a mean of 5.6 years, 3.4% (5/147) had PH confirmed by RHC, and among these patients, 2 had isolated PAH and 3 had PH associated with ILD.[238] A UK registry study of all incident CTD-PH cases over a 5-year period identified 36 cases for MCTD-PH among 60 million individuals.[5] Moreover, a Korean registry study of 174 incident cases of CTD-PH found that 6% of CTD-PH patients had MCTD.[239]

The aforementioned findings contrast with previous studies in MCTD reporting prevalence rates between 19 and 24%.[240–242] Discrepancies in prevalence rates may be attributable to differences in MCTD disease criteria utilized, varying follow-up periods, and how the investigators screened and diagnosed PH (i.e., echocardiography vs. RHC).

Minimal data exists on treatment outcomes for MCTD-PH. A small study of eight patients with MCTD found that three patients demonstrated a functional and/or hemodynamic improvement with immunosuppressant therapy (IV CYC and glucocorticoids) without a need for PH-specific therapy.[7] In a series of 10 patients with MCTD-associated PH, 7 were initially treated with IST alone, with 4 responders (57%).[243] Three patients were *initially* treated with *both* IST and pulmonary vasodilators, with two responses (67%).

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 IST or for patients with severe disease.

Summary

Among the CTDs, PH occurs most commonly in the setting of SSc. However, PH can develop in SLE and MCTD (rarely in rheumatoid arthritis and Sjögren's syndrome). Although PH is a leading cause of morbidity and mortality in patients with CTD, the impact of PH specific and IST on treatment-related outcomes is unclear. Prospective studies are needed to investigate the safety and efficacy of therapy for managing this important clinical dimension of CTD.

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