Non-Group 1 Pulmonary Hypertension Associated With Systemic Sclerosis: An Under-studied Patient Population

Zafia Anklesaria, MD
Department of Medicine
Division of Pulmonary and Critical Care
University of California, Los Angeles
Los Angeles, CA

Rajeev Saggar, MD
Lung institute
Banner University Medical Center
University of Arizona, Phoenix
Phoenix, AZ

Ariss Derhovanessian, MD
Department of Medicine
Division of Pulmonary and Critical Care
University of California, Los Angeles
Los Angeles, CA

Rajan Saggar, MD
Department of Medicine
Division of Pulmonary and Critical Care
University of California, Los Angeles
Los Angeles, CA

Background: Systemic sclerosis (SSc) is a heterogeneous disorder that results in multiorgan dysfunction. The most common pulmonary manifestations are pulmonary hypertension (PH) and interstitial lung disease (ILD). Systemic sclerosis may be complicated by World Health Organization (WHO) Group 1 PH (SSc-PAH), which is the most well-studied subtype. The PH associated with SSc may also be secondary to underlying left heart disease (SSc-PH-LHD) or ILD (SSc-PH-ILD), and these subgroups are classified as WHO Group 2 and Group 3 PH, respectively. These non-WHO Group 1 PH subsets are notoriously under-studied. Available data suggest that the impact of PH-specific therapy in SSc-PH-LHD and SSc-PH-ILD is limited and survival is poor despite attempted treatment.
Implication for clinicians: Most research and clinical trials surrounding PH in SSc have thus far focused on WHO Group 1 SSc-PAH. There are limited data surrounding therapeutic options for WHO Group 2 (SSc-PH-LHD) and Group 3 PH (SSc-PH-ILD) phenotypes. This review aims to summarize and consolidate the data surrounding these 2 distinct clinical phenotypes and to emphasize the available prognostic and treatment considerations.
Conclusions: Given the unique pathophysiology, prognostic implications, and poor response to treatment of WHO Group 2 and 3 SSc-PH phenotypes, there is an overwhelming need for more data to best understand optimal management strategies. The focus should be individual patient-level prognostication, how and when to initiate and manage PH-specific therapy, and appropriate triage with regard to the timing of lung (or heart-lung) transplantation.

Systemic sclerosis (SSc) is a heterogeneous disorder characterized by endothelial and fibroblast dysregulation, as well as immune dysfunction leading to excess of collagen deposition resulting in fibrosis of multiple organ systems.[1] Systemic sclerosis may manifest as either limited cutaneous or diffuse cutaneous SSc; the latter typically has more extensive skin fibrosis and organ involvement. Beyond the skin, commonly involved organ systems include renal, cardiac, gastrointestinal, and pulmonary systems. Pulmonary involvement is the leading cause of mortality in SSc and occurs most frequently in the form of interstitial lung disease (ILD) and/or pulmonary hypertension (PH). Interstitial lung disease is more common in diffuse SSc,[2] while those with limited SSc have a higher likelihood of developing PH.[3] Over time, both PH and pulmonary fibrosis (PF) have emerged as leading causes of death in SSc.[4]

Not all PH associated with SSc falls under World Health Organization (WHO) Group 1 (SSc-PAH). Significant portions have underlying left heart disease (SSc-PH-LHD) or ILD (SSc-PH-ILD) associated with PH and are categorized under WHO Group 2 and Group 3 PH, respectively. Of these, SSc-PAH has been the most extensively studied. When compared to idiopathic pulmonary arterial hypertension (IPAH), SSc-PAH carries a 3-fold increased risk of death and a worse response to PH-specific therapy despite having more favorable baseline hemodynamics.[5] The ASPIRE registry (UK experience) reports a 3-year survival rate of 63% for IPAH compared to 52% for SSc-PAH.[6] The 3 different types of PH associated with SSc are distinct clinical entities and require special consideration for prognostication and management. This review aims to discuss the evidence surrounding the 2 less well-studied subgroups of SSc-PH: SSc-PH-LHD (WHO Group 2) and SSc-PH-ILD (WHO Group 3).

Key Words—heart failure with preserved ejection fraction, interstitial lung disease, pulmonary hypertension, systemic sclerosis
Correspondence: rsaggar@mednet.ucla.edu
Disclosures: The authors have nothing to disclose.

GROUP 3 PH IN SCLERODERMA (SSC-PH-ILD)

Epidemiology and Prognostic Implications

Interstitial lung disease is a well-recognized complication of several connective tissue diseases (CTD). Studies of radiographic features, pulmonary function test (PFT) parameters, and pathologic abnormalities suggest that ILD is the most common pulmonary manifestation of SSc, with approximately 40% of patients demonstrating a restrictive pattern on PFTs and up to 90% having pathologic evidence of PF at the time of autopsy.[7,8] Radiographic features of ILD on high-resolution computed tomog-

raphy (HRCT) chest scans are present in 55% to 65% of SSc cohorts and in 96% of those with restrictive pulmonary function testing.[7,9]

The prevalence of SSc-ILD with PH is reported as 18% to 22%, which is similar to the prevalence of SSc-PAH, and is consistent among similar cohorts.[10,11] In the ASPIRE registry of 323 patients with PH associated with a CTD (83% of which were SSc), 31% had PH-ILD.[6] SSc-PH-ILD appears to be associated with an older age at diagnosis, severe restriction (forced vital capacity <50%), and a lower arterial oxygen tension compared to SSc-PAH.[10,11] It should be noted that HRCT chest features of ILD, such as septal lines and/or centrilobular ground glass opacities, may also be present in WHO Group 1 PAH, perhaps making the distinction between SSc-PAH and SSc-PH-ILD challenging.[12]

Interstitial lung disease in general requires good therapeutic triage, which includes prognostication and timing of listing for lung transplantation. The reported median survival for SSc-ILD is 5 to 8 years after diagnosis.[13] It remains well established that the presence of pulmonary vascular disease is a poor prognostic factor in fibrotic lung disease. In fact, an elevated systolic pulmonary artery pressure (sPAP) and pulmonary vascular resistance (PVR) determined by right heart catheterization (RHC) in idiopathic pulmonary fibrosis (IPF) correlates inversely with survival, while pulmonary function parameters have generally not predicted mortality.[14] Similarly, the prognosis for SSc-ILD complicated by PH is particularly grim.[15]

There are some conflicting data regarding mortality when SSc-PAH is compared to SSc-PH-ILD; however, the majority of cohorts demonstrate significantly increased mortality in SSc-PH-ILD. Chang et al noted no significant difference in survival between SSc-PAH (defined by echocardiography) and SSc-PH-ILD.[10] In contrast, a multivariate analysis showed that SSc-PH-ILD (defined by RHC parameters) was found to be associated with a 5-fold increase in mortality when compared to SSc-PAH.[16] The same study noted a 3-year survival rate of 64% in SSc-PAH compared to 39% in SSc-PH-ILD. The difference in reported mortality between these 2 studies was likely because estimates of right ventricular systolic pressure (RVSP) by echocardiography are not as accurate or precise as RHC measurements, especially in the setting of parenchymal lung disease.[17] In support of the latter study, Condliffe et al reported a 3-year survival rate of 47% in SSc-PAH compared to 28% in SSc-PH associated with respiratory disease in a UK registry approach.[18] Similarly, the ASPIRE registry reported a 3-year survival rate of 54% for Group 1 PAH associated with CTD in contrast to 40% for PH-ILD associated with CTD.[6]

These reported differences in mortality rates highlight the importance of defining and understanding the combined PH-ILD phenotype in SSc. Unfortunately this subset is routinely excluded from clinical trials of PH-specific therapy.

Pathophysiology

The pathophysiology of PH in chronic lung disease is complex and poorly understood. Prior studies have postulated that hypoxic vasoconstriction and chronic inflammation lead to increased tone and muscularization of small pulmonary arteries resulting in epithelial damage, small vessel destruction, and fibrosis. Thus, chronic hypoxemia may trigger vascular remodeling resulting in increased PVR.[19] In IPF, the resultant epithelial damage from chronic hypoxemia and lung architectural distortion has been shown to result in fibroblast activation and eventual endothelial apoptosis, resulting in decreased vascular density and the release of growth factors that promote vascular remodeling.[20,21] Higher serum levels of endothelin-1 (ET-1), a potent vasoconstrictor known to enhance mitogenesis and promote extracellular matrix formation, were found to be associated with higher sPAP and PVR in IPF.[22] In SSc, the underlying mechanisms that drive PH appear to be even more complex. Chronic inflammation and oxidative damage from immune complex-mediated endothelial injury are thought to contribute to damage of the extracellular matrix. In addition, autoantibodies may promote endothelial apoptosis resulting in destruction of the vascular bed.[23] Increased plasma ET-1 levels in SSc also likely contribute to the vasoconstriction and vascular remodeling causing PH.[24]

Several groups have noted differences in mortality rates and response to treatment in SSc-PAH when compared to IPAH. These findings may be explained by the underlying vascular pathology. Overbeek et al examined the pulmonary microcirculation and determined that both IPAH and SSc-PAH demonstrated arteriopathy; however, SSc-PAH was distinguished by the lack of plexiform lesions and the presence of a superimposed veno-occlusive pattern with capillary duplication.[25] In another study of CTD-associated PH, similar vascular pathology was noted.[26] Colombat et al also reported veno-occlusive pathology in architecturally preserved areas of IPF lungs, but they were unable to find a relationship between this pathologic lesion and RHC-determined PH.[27] While pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are each distinctly classified as their own subgroup within WHO Group 1 PH, components of their unique histopathology may also be seen in PH associated with SSc and other CTDs. Capillary duplication (defined as an abnormal proliferation of capillaries more than 2 layers thick), which characterizes PCH, has also been described in the context of PVOD, presumably as a secondary consequence of downstream obstruction.[28] There is therefore considerable heterogeneity in the pathogenic basis for PH in the setting of SSc-ILD and the defining elements remain unknown. Similar to IPF, parenchymal fibrosis and chronic inflammation may lead to destruction of the pulmonary vasculature and/or hypoxia-induced vascular remodeling. In addition, a distinct fibroproliferative vasculopathy affecting the entire pulmonary microcirculation may be present. It remains unclear if a histopathologic element of the pulmonary microcirculation exists that distinguishes SSc-ILD with, as compared to without, PH. Finally, it is notoriously difficult to study vascular remodeling in the setting of fibrotic lung disease because of difficulty in distinguishing

small arteries and veins due to loss of normal lung architecture.[29] In order to overcome this obstacle and adequately examine the vascular bed, studies need to be done on whole lung specimens from SSc-ILD patients, perhaps with a focus on the architecturally preserved areas of lung tissue.

Pulmonary hypertension in the setting of SSc-ILD is often "out of proportion" to that expected from SSc-ILD based on the severity of the ILD alone. A significant portion (up to 25%) of patients with SSc-PH-ILD have a mean pulmonary artery pressure (mPAP) >35 mm Hg,[30] suggesting an underlying combined pathology derived from both SSc-PAH and SSc-ILD. The multifaceted pathophysiology and lack of sound studies on pathology cohorts of SSc-PH-ILD highlight the special consideration and expertise necessary to consider PH-specific therapy in such patients. It also emphasizes the need for more data regarding the changes in the pulmonary microcirculation, which are inherent to the development of clinical PH.

Treatment Considerations

There is limited evidence supporting the use of PH-specific therapy in SSc-PH-ILD. This subgroup is often excluded from studies because of a fear that the use of pulmonary vasodilators may increase ventilation/perfusion (V/Q) mismatch by disabling the protective mechanism of pulmonary hypoxic vasoconstriction. Thus, while PH-specific therapy could potentially improve pulmonary hemodynamics, arterial oxygenation may be compromised.[31] This concern is reflected in the fact that pulmonary vasodilators, particularly prostanoids, are rarely used in SSc-PH-ILD cohorts.[16] Several studies have propagated this concern. For example, in the Artemis IPF study, the investigators aimed to determine if ambrisentan would reduce the rate of IPF progression. The study was terminated early due to unacceptable disease progression and respiratory hospitalizations in the group treated with ambrisentan; this finding was independent of the presence of PH.[32] A study of *acute* administration of sildenafil in PH secondary to ILD was reported and compared to inhaled nitric oxide and intravenous (IV) epoprostenol. It was noted that while all 3 interventions decreased PVR, IV epoprostenol worsened both oxygenation and V/Q matching, while sildenafil and inhaled nitric oxide improved oxygenation and maintained V/Q matching.[33] In support of these data, the STEP-IPF trial showed that in advanced IPF, sildenafil improved oxygenation compared to placebo, but did not improve the primary endpoint of 6-minute walk distance (6MWD).[34] Interestingly, a subgroup analysis of the STEP-IPF study demonstrated that sildenafil (compared to placebo) significantly improved 6MWD in the cohort of IPF patients with right ventricular (RV) dysfunction at baseline.[35] Another study of acute administration of parenteral prostacyclin analogs in PH secondary to fibrotic lung disease showed a decrease in mPAP with an associated worsening V/Q mismatch and hypoxemia. In the same study, inhaled prostacyclin analogs did not worsen oxygenation or V/Q matching.[36] Thus, in the setting of PF with PH, sildenafil and inhaled prostacyclins may have relatively favorable profiles with regard to pulmonary hemodynamics and oxygenation, compared to parenteral prostacyclins.

As discussed, SSc-PAH appears to be characterized by a distinct pan-vasculopathy with PVOD-like lesions.[25] It is possible that similar pathology plays a role in SSc-PH-ILD and may be responsible for the detrimental effect of parenteral prostanoid therapy in this subgroup. Montani et al reported the development of pulmonary edema with different classes of PH-specific therapy in classic PVOD.[37] The putative mechanism suggests PH-specific therapy promotes vasodilation in the precapillary bed and, in the setting of increased downstream resistance in the pulmonary veins, results in elevated transcapillary hydrostatic pressure, which may result in pulmonary edema.[37] However, in some cases of classic PVOD, the cautious use of continuous IV epoprostenol may actually improve pulmonary hemodynamics and thus can selectively be considered as a therapeutic option.[38] With regard to SSc-related PH, investigators at L'Hopital Antoine Béclère in France reported their experience with bosentan therapy. They observed significant improvement in functional class and hemodynamics; however, in the subgroups of SSc-ILD (no PH) and SSc-PH-ILD, no clear benefits were noted.[39,40] In a combined Johns Hopkins and French experience, 70 cases of SSc-PH-ILD were studied to determine the impact of PH-specific therapies including inhaled and IV prostacyclin, endothelin receptor antagonists, and phosphodiesterase type 5 (PDE-5) inhibitors and found no clear benefit with regard to pulmonary hemodynamics. In fact, the same authors found a signal for worsening hypoxemia and decreased survival, particularly in those with a reduced diffusion lung capacity for carbon monoxide (DLCO) or those who used supplemental oxygen at baseline. It is thus unclear whether the observed decrease in oxygenation and survival was a result of PH-specific therapy or simply worsening pulmonary fibrosis.[41]

More recently, there is some evidence supporting the use of pulmonary vasodilators in PH secondary to PF (idiopathic or CTD-related). As proof of concept, Saggar et al studied PH-ILD with advanced pulmonary hemodynamics (mPAP ≥35 mm Hg) and demonstrated that chronic parenteral treprostinil improved pulmonary hemodynamics without affecting systemic oxygenation. In addition, there were congruent improvements in RV function, brain natriuretic peptide (BNP), 6MWD, and the mental component summary (MCS) aggregate of the short form (SF)-36.[42] Notably, this study excluded PH-ILD secondary to SSc. To build on this concept, the same authors retrospectively evaluated the effects of aggressive PH-specific therapy (defined as combination therapy or parenteral prostanoid therapy) in SSc-PH and SSc-PH-ILD and found that in addition to comparable survival between these 2 phenotypes, the use of early and aggressive parenteral prostanoid therapy (initiated within 6 months of diagnosis of PH) was associated with improved transplant-free survival in the SSc-PH-ILD group compared to prior reports.[43] Unfortunately this study lacked a control group of SSc-PH-ILD not receiving PH-specific

therapy. Nevertheless, these data suggest that in the appropriate setting (advanced pulmonary hemodynamics and RV dysfunction) and in a center with expertise, PH-specific therapy may have a role in selected cases of SSc-PH-ILD.

An observational study by Condliffe et al suggested that despite treatment with PH-specific therapy, survival in SSc with WHO Group 3 PH was significantly worse than SSc-PAH, and reported that a subgroup of the WHO Group 3 PH population seemingly demonstrated "out-of-proportion" PH relative to the degree of underlying lung fibrosis.[18] Le Pavec et al also addressed this concept by analyzing the response to PH-specific therapy in the subset of SSc-PH-ILD with mPAP >40 mm Hg, but found no difference when compared to the group with mPAP <40 mm Hg.[41]

It is clear that survival in SSc-PH-ILD is poor, but despite this disadvantage, this subgroup remains under-studied due to the fear of worsening gas exchange and the potential for acute pulmonary edema with PH-specific therapy. Proof-of-concept studies suggest that perhaps early and aggressive use of PH-specific therapy may not negatively impact systemic oxygenation and may improve right ventricular and pulmonary arterial coupling. Regardless, an in-depth understanding of the pathophysiology active in the SSc-PH-ILD phenotype, specifically the possibility of a vasculopathy affecting the entire pulmonary microcirculation, is important, especially if considering a trial of PH-specific therapy. Given the lack of an established role for PH-specific therapy, early referral to a lung transplantation center is critical given the poor prognosis and is the treatment of choice. [44]

GROUP 2 PH IN SCLERODERMA (SSC-PH-LHD)

Epidemiology and Prognostic Considerations

The PH associated with SSc can be secondary to underlying left heart disease (SSc-PH-LHD). Pulmonary venous hypertension (PVH) or postcapillary PH is defined by the presence of PH (mPAP >25 mm Hg) combined with a pulmonary artery wedge pressure (PAWP) >15 mm Hg (Table 1).[45] This hemodynamic profile is classified as SSc-PH-LHD, which is a subset of WHO Group 2 PH. The PH that results from LHD may be clinically categorized into heart failure associated with reduced ejection fraction (HFrEF), preserved ejection fraction (HFpEF), valvular disease, or congenital heart disease.[46] The ASPIRE registry reported that 10% of all SSc-PH is classified as PH-LHD when assessed by a combination of echocardiography and cardiac magnetic resonance imaging (MRI).[6] If PAWP is employed as the only distinguishing feature between pre- and postcapillary PH, then most studies suggest that SSc-PH-LHD is less prevalent than SSc-PAH, with the caveat that PAWP is a preload-dependent variable.[47] In fact, within a large cohort of SSc-PH (>7600 subjects), 45% had a PAWP >15 mm Hg.[48] Another study reported a lower prevalence of elevated PAWP (20.5%) within an SSc-PH cohort, but excluded those with known decreased systolic function.[49] Alternatively, a case control study of the EUSTAR database revealed that 50% of cases with left ventricular (LV) dysfunction (LVEF <55%) had an sPAP >40 mm Hg by echocardiogram, which may be expected given the tendency for pulmonary venous congestion with low LVEF. The authors report that based on RHC, approximately 29% of these cases demonstrated "precapillary" PH (Table 1).[50] A meta-analysis revealed that of the SSc-PH confirmed by RHC, nearly

Table 1. Features of the 3 Subgroups of PH Associated With SSc

	SSc-PAH	SSc-PH-ILD	SSc-PH-LHD
Definition	- WHO Group 1 PH associated with SSc - Precapillary PAH mPAP ≥25 mm Hg, PAWP ≤15 mm Hg[45]	- WHO Group 3 PH associated with SSc - Precapillary PH with radiographic and/or PFT evidence of ILD[45] mPAP ≥25 mm Hg, PAWP≤15 mm Hg[45]	- WHO Group 2 PH associated with left heart disease, most commonly HFpEF - Postcapillary PH or pulmonary venous hypertension mPAP ≥25 mm Hg, PAWP >15 mm Hg[45] - Isolated postcapillary PH DPG <7 mm Hg, PVR ≤3 WU[45]
Prevalence	7%-18% of SSc cohorts[10,11] ~50% of SSc-PH[6,47]	18%-22% of SSc cohorts[10,11] ~25% of SSc-PH[6]	Postcapillary PH: 10%-45% of SSc-PH[6,47,48] Isolated postcapillary PH: 20% of SSc-PH[47]
Mortality	47%-64% 3-year survival[6,16,18]	16%-40% 3-year survival.[6,16,18] 5-fold increased risk of death compared to SSc-PAH[16]	73% 3-year survival[6]
Pathobiology	Predominant arteriopathy with noted veno-occlusive lesions and capillary duplication[25,26,29]	Hypoxic vasoconstriction and remodeling[19]; thus far, unreported histopathology	Stress injury to alveolar capillary membrane; pulmonary artery intimal fibrosis and medial hypertrophy[64,65]

Abbreviations: DPG: diastolic pulmonary gradient; HFpEF: heart failure with preserved ejection fraction; ILD: interstitial lung disease; mPAP: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure; PFT: pulmonary function testing; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; SSc: systemic sclerosis; WU: Wood units.

80% had precapillary PH and only 20% had "postcapillary" PH (Table 1), again suggesting that within SSc-PH, SSc-PH-LHD is less common than SSc-PAH.[47] This is in contrast to PH not associated with SSc, where PH-LHD is the most common among WHO groups.[51]

Systemic sclerosis has myriad cardiac manifestations; the cardiac involvement is usually direct, but may also be a secondary phenomenon due to pulmonary or renal disease and, either way once clinically apparent, it has a poor prognosis. In addition to patchy myocardial fibrosis characteristically involving the subendocardial layer, other cardiac structures can be affected including the coronary circulation, conduction system, and pericardium.[52] Autopsy studies have noted myocardial fibrosis and pericardial involvement to be the most prevalent, with clinical evidence of myocardial disease present 20% to 25% of the time, manifesting as systolic and/or diastolic LV dysfunction.[53]

Cardiac involvement in SSc is likely underestimated due to nonspecific symptomatology, and prevalence reports vary depending on the method of detection used to define cardiac involvement. For example, by echocardiography, 69% of an SSc cohort was found to have at least one or more of the following: elevated RVSP, pericardial effusion, increased RV dimension, or left atrial enlargement (LAE).[54] Left ventricular systolic dysfunction (LVEF <55%) is rarely reported with an estimated prevalence of only 1.4% to 5.4% in SSc cohorts,[48,55] while diastolic dysfunction and left ventricular hypertrophy are reported in 18% and 23%, respectively.[55] In contrast to echocardiography, cardiac MRI provides additional information with regard to myocardial fibrosis. Cardiac MRI with contrast enhancement detected abnormalities in 75% of an SSc cohort, including systolic and/or diastolic dysfunction as well as the extent of myocardial fibrosis and inflammation.[56] An analysis of global organ involvement in SSc revealed diastolic dysfunction as one of the most frequent features of the disease with a prevalence of 17.4%.[48] Thus, HFpEF appears to be the most common cardiac manifestation of SSc and as such, PH secondary to HFpEF (PH-HFpEF) is the most common subgroup of SSc-PH-LHD.

In general, HFpEF is the most common subtype of WHO Group 2 PH. Lam et al noted that up to 80% of patients with HFpEF have echocardiographic evidence of elevated estimated RVSP consistent with PH.[57] Furthermore, several studies have demonstrated that when PH and/or RV dysfunction complicates HFpEF of any cause, outcomes are inferior compared to isolated HFpEF. For example, one study reported an increased risk of hospitalizations and all-cause mortality in PH-HFpEF in comparison to HFpEF without PH.[58] Furthermore, Lam et al reported that each 10 mm Hg increase in estimated RVSP by echocardiogram was associated with a 1.2-fold increased risk of death, independent of age.[59] Kjaergaard et al studied 334 patients with WHO Group 2 PH, 90% of whom had PH-HFpEF; they recorded 1- and 2-year survival estimates of 82% and 74% respectively, and noted that a PASP >39 mm Hg was associated with increased mortality.[60] Unfortunately, while these studies highlight the importance of PH-HFpEF as a clinically relevant phenotype with a poor prognosis, similar studies comparing HFpEF with and without PH are not available in the setting of SSc.

In general, survival of Group 2 PH is superior to Group 1 and Group 3 PH. The ASPIRE registry reports a 3-year survival of 68% for Group 3 PH and 44% for Group 1 PAH. They reported similar 3-year survival statistics for CTD-PAH (54%) and CTD-PH-LHD (73%).[6] However, an elevated PAWP has been shown to independently generate an additional pulsatile load on the RV in the setting of a variety of PH etiologies.[61] Interestingly, the Johns Hopkins group compared SSc-PAH to SSc-PH-HFpEF (defined by PAWP >15 mm Hg and preserved systolic function) and found that SSc-PH-HFpEF had worse hemodynamic impairment and a 2-fold increased risk of death when controlling for hemodynamic parameters that are known to affect prognosis,[49] and was unaltered by the use of PH-specific therapy. In fact, SSc-PH-HFpEF demonstrated a higher mPAP and a similar transpulmonary gradient (TPG) compared to SSc-PAH, possibly because of intrinsic pulmonary vascular disease superimposed on the increased pulsatile load intrinsic to elevated PAWP in this SSc cohort. Furthermore, the authors did note that within the subgroups of SSc-PH-HFpEF, survival in the group with "isolated postcapillary PH" was superior to the group with combined "pre- and postcapillary PH." It therefore seems that SSc-PH-HFpEF may portend a worse prognosis than SSc-PAH, making it important to define the presence and extent of left heart disease in SSc-PH for both prognostic and treatment considerations.

Distinguishing between pre-, post- and combined "pre- and postcapillary" PH is challenging given that RHC hemodynamics may be dependent on volume status and operator interpretation. Studies on HFpEF as well as SSc-HFpEF have demonstrated that a 0.5-liter fluid bolus during RHC may unmask occult postcapillary PH in up to 20% of patients and thus reclassify precapillary PH as combined "pre- and postcapillary" PH.[62,63] It is clear that obtaining accurate hemodynamic measurements and subsequently classifying patients into the appropriate SSc-PH subgroup requires expertise, especially given the potential for significant overlap. Scant data on this subject exist; nevertheless, understanding an individual patient's physiology is imperative as it clearly governs subsequent management decisions.

Pathophysiology

Isolated postcapillary PH is the result of a passive increase in PAP without fixed pulmonary arterial vasoconstriction or remodeling. This increase is usually proportionate to the increase in left-sided filling pressure with normal PVR and TPG. However, chronically increased left-sided filling pressure can trigger pulmonary arterial vasoconstriction and intrinsic remodeling, which may result in a hemodynamic picture consistent with combined "pre- and postcapillary" PH. At the level of the pulmonary microvasculature, changes may include medial hypertrophy and intimal fibro-

sis of small pulmonary arteries as well as thickening and remodeling of the alveolar capillary membrane.[64,65] The angioproliferative plexiform lesions characteristic of IPAH are rare. In addition, matrix metalloproteinases are activated by increased left-sided filling pressures causing stress injury to the alveolar capillary membrane over time, and may result in alveolar wall fibrosis and extracellular matrix deposition.[65]

Treatment Considerations

Current guidelines[45] do not recommend PH-specific therapy for the treatment of WHO Group 2 PH. Management should be focused on careful diagnostics (identification of the underlying cause and careful assessment of pulmonary hemodynamics) and treatment of the underlying condition. In aggregate, studies of PH-specific therapies in both PH-HFrEF and PH-HFpEF have not been able to confirm benefit. For example, in a small study of PH-HFpEF and a randomized placebo-controlled study of HFrEF, sildenafil improved hemodynamics and symptoms,[66,67] but in a larger randomized control trial of HFpEF with and without PH, no benefits of sildenafil were seen.[68] In HFrEF, IV epoprostenol showed a trend toward increased mortality.[69] The ENABLE trial examined the effect of bosentan on severe heart failure (mean LVEF 25%) and revealed no advantage over placebo with regard to hospitalization or time to death.[70] Soluble guanylate cyclase (sGC) stimulators have been shown to have antiproliferative and anti-inflammatory effects in animal models,[71] suggesting that they may be of benefit in PH associated with HFrEF and HFpEF. The LEPHT and DILATE-1 trials support this theory by showing that riociguat may result in a small decrease in mPAP. The significance of this finding is yet uncertain, but it suggests that targeting the nitric oxide-sGC-cyclic guanosine monophosphate pathway may be beneficial in Group 2 PH.[72,73] Unfortunately, most prior studies failed to stratify subjects according to hemodynamics, nor did they separate out those with and without PH. Furthermore, the underlying cause of the left heart disease was not often clarified. To date, there are no known studies specifically studying Group 2 PH in the setting of SSc. There is a continued need for further research in this area, particularly with regard to PH-HFpEF, as this is the most prevalent type of Group 2 PH. In addition, careful delineation of the PH as either pre-, post- or "pre- and postcapillary" is helpful in determining whether there may be merit in considering a trial of PH-specific therapy.

CONCLUSION

Pulmonary hypertension is among the leading causes of mortality in SSc and is heterogeneous with regard to pathophysiology and treatment considerations. The different types of PH complicating SSc require nuanced understanding with regard to diagnosis, prognostication, and management. Given that the prognosis of all groups of SSc-PH is poor and therapy is of limited known utility, additional studies are needed to optimize the management of this condition.

References

1. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. *Ann Intern Med*. 2004;140(1):37-50.
2. Steen V. Predictors of end stage lung disease in systemic sclerosis. *Ann Rheum Dis*. 2003;62(2):97-99.
3. Steen V, Medsger TA Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum*. 2003;48(2):516-522.
4. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis*. 2007;66(7):940-944.
5. Fisher MR, Mathai SC, Champion HC, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum*. 2006;54(9):3043-3050.
6. Hurdman J, Condliffe R, Elliot CA, et al. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. *Eur Respir J*. 2012;39(4):945-955.
7. Diot E, Boissinot E, Asquier E, et al. Relationship between abnormalities on high-resolution CT and pulmonary function in systemic sclerosis. *Chest*. 1998;114(6):1623-1629.
8. D'Angelo WA, Fries JF, Masi AT, Shulman LE. Pathologic observations in systemic sclerosis (scleroderma). A study of fifty-eight autopsy cases and fifty-eight matched controls. *Am J Med*. 1969;46(3):428-440.
9. Schurawitzki H, Stiglbauer R, Graninger W, et al. Interstitial lung disease in progressive systemic sclerosis: high-resolution CT versus radiography. *Radiology*. 1990;176(3):755-759.
10. Chang B, Wigley FM, White B, Wise RA. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. *J Rheumatol*. 2003;30(11):2398-2405.
11. Launay D, Mouthon L, Hachulla E, et al. Prevalence and characteristics of moderate to severe pulmonary hypertension in systemic sclerosis with and without interstitial lung disease. *J Rheumatol*. 2007;34(5):1005-1011.
12. Rajaram S, Swift AJ, Condliffe R, et al. CT features of pulmonary arterial hypertension and its major subtypes: a systematic CT evaluation of 292 patients from the ASPIRE Registry. *Thorax*. 2015;70(4):382-387.
13. Altman RD, Medsger TA Jr, Bloch DA, Michel BA. Predictors of survival in systemic sclerosis (scleroderma). *Arthritis Rheum*. 1991;34(4):403-413.
14. Corte TJ, Wort SJ, Gatzoulis MA, Macdonald P, Hansell DM, Wells AU. Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected pulmonary hypertension. *Thorax*. 2009;64(10):883-888.
15. Trad S, Amoura Z, Beigelman C, et al. Pulmonary arterial hypertension is a major mortality factor in diffuse systemic sclerosis, independent of interstitial lung disease. *Arthritis Rheum*. 2006;54:184-191.
16. Mathai SC, Hummers LK, Champion HC, et al. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. *Arthritis Rheum*. 2009;60(2):569-577.
17. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med.* 2003;167(5):735-740.
18. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med*. 2009;179(2):151-157.
19. Stenmark KR, Fagan KA, Frid MG. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. *Circ Res*. 2006;99(7):675-691.
20. Farkas L, Gauldie J, Voelkel NF, Kolb M. Pulmonary hypertension and idiopathic pulmonary fibrosis: a tale of angiogenesis, apoptosis, and growth factors. *Am J Respir Cell Mol Biol*. 2011;45(1):1-15.
21. Farkas L, Farkas D, Ask K, et al. VEGF ameliorates pulmonary hypertension through inhibition of endothelial apoptosis in experimental lung fibrosis in rats. *J Clin Invest*. 2009;119(5):1298-1311.
22. Ventetuolo CE, Kawut SM, Lederer DJ. Plasma endothelin-1 and vascular endothelial growth factor levels and their relationship to hemodynamics in idiopathic pulmonary fibrosis. *Respiration*. 2012;84(4):299-305.
23. Guiducci S, Distler O, Distler JH, Matucci-Cerinic M. Mechanisms of vascular damage in SSc--implications for vascular treatment strategies. *Rheumatology (Oxford)*. 2008;47 Suppl 5:v18-v20.

24. Sgonc R, Gruschwitz MS, Dietrich H, Recheis H, Gershwin ME, Wick G. Endothelial cell apoptosis is a primary pathogenetic event underlying skin lesions in avian and human scleroderma. *J Clin Invest*. 1996;98(3):785-792.
25. Overbeek MJ, Vonk MC, Boonstra A, et al. Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. *Eur Respir J*. 2009;34(2):371-379.
26. Dorfmuller P, Humbert M, Perros F, et al. Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. *Hum Pathol*. 2007;38(6):893-902.
27. Colombat M, Mal H, Groussard O, et al. Pulmonary vascular lesions in end-stage idiopathic pulmonary fibrosis: Histopathologic study on lung explant specimens and correlations with pulmonary hemodynamics. *Hum Pathol*. 2007;38(1):60-65.
28. Girgis RE, Mathai SC. Pulmonary hypertension associated with chronic respiratory disease. *Clin Chest Med*. 2007;28(1):219-232.
29. Tuder RM, Archer SL, Dorfmuller P, et al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D4-D12.
30. Mukerjee D, St George D, Coleiro B, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis*. 2003;62(11):1088-1093.
31. Simonneau G, Escourrou P, Duroux P, Lockhart A. Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. *N Engl J Med*. 1981;304(26):1582-1585.
32. Raghu G, Behr J, Brown KK, et al; ARTEMIS-IPF Investigators. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Ann Intern Med*. 2013;158(9):641-649.
33. Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet*. 2002;360(9337):895-900.
34. Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwart M, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med*. 2010;363(7):620-628.
35. Han MK, Bach DS, Hagan PG, et al; IPFnet Investigators. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. *Chest*. 2013;143(6):1699-1708.
36. Olschewski H, Ghofrani HA, Walmrath D, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. *Am J Respir Crit Care Med*. 1999;160(2):600-607.
37. Montani D, Achouh L, Dorfmuller P, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine (Baltimore)*. 2008;87(4):220-233.
38. Okumura H, Nagaya N, Kyotani S, et al. Effects of continuous IV prostacyclin in a patient with pulmonary veno-occlusive disease. *Chest*. 2002;122(3):1096-1098.
39. Launay D, Sitbon O, Le Pavec J, et al. Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. *Rheumatology (Oxford)*. 2010;49(3):490-500.
40. Seibold JR, Denton CP, Furst DE, et al. Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis. *Arthritis Rheum*. 2010;62(7):2101-2108.
41. Le Pavec J, Girgis RE, Lechtzin N, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. *Arthritis Rheum*. 2011;63(8):2456-2464.
42. Saggar R, Khanna D, Vaidya A, et al. Changes in right heart haemodynamics and echocardiographic function in an advanced phenotype of pulmonary hypertension and right heart dysfunction associated with pulmonary fibrosis. *Thorax*. 2014;69(2):123-129.
43. Volkmann ER, Saggar R, Khanna D, et al. Improved transplant-free survival in patients with systemic sclerosis-associated pulmonary hypertension and interstitial lung disease. *Arthritis Rheumatol*. 2014;66(7):1900-1908.
44. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2015;34(1):1-15.
45. Galiè N, Humbert M, Vachiery JL, et al.2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.
46. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-D41.
47. Avouac J, Airo P, Meune C, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *J Rheumatol*. 2010;37(11):2290-2298.
48. Meier FM, Frommer KW, Dinser R, et al; EUSTAR Co-authors. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. *Ann Rheum Dis*. 2012;71(8):1355-1360.
49. Bourji KI, Kelemen BW, Mathai SC, et al. Poor survival in patients with scleroderma and pulmonary hypertension due to heart failure with preserved ejection fraction. *Pulm Circ*. 2017;7(2):409-420.
50. Allanore Y, Meune C, Vonk MC, et al; EUSTAR co-authors. Prevalence and factors associated with left ventricular dysfunction in the EULAR Scleroderma Trial and Research group (EUSTAR) database of patients with systemic sclerosis. *Ann Rheum Dis*. 2010;69(1):218-221.
51. Guazzi M, Arena R. Pulmonary hypertension with left-sided heart disease. *Nat Rev Cardiol*. 2010;7(11):648-659.
52. Weiss S, Stead E, Warren J. Scleroderma heart disease, with a consideration of certain other visceral manifestations of scleroderma. *Arch Intern Med*. 1943;71:1.
53. Follansbee WP, Miller TR, Curtiss EI, et al. A controlled clinicopathologic study of myocardial fibrosis in systemic sclerosis (scleroderma). *J Rheumatol*. 1990;17(5):656-662.
54. Smith JW, Clements PJ, Levisman J, Furst D, Ross M. Echocardiographic features of progressive systemic sclerosis (PSS). Correlation with hemodynamic and postmortem studies. *Am J Med*. 1979;66(1):28-33.
55. de Groote P, Gressin V, Hachulla E, et al; ItinerAIR-Scleroderma Investigators. Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis. *Ann Rheum Dis*. 2008;67(1):31-36.
56. Hachulla AL, Launay D, Gaxotte V, et al. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. *Ann Rheum Dis*. 2009;68(12):1878-1884.
57. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol*. 2009;53(13):1119-1126.
58. Mohammed SF, Hussain I, AbouEzzeddine OF, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. *Circulation*. 2014;130(25):2310-2320.
59. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation*. 2009;119(20):2663-2670.
60. Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. *Am J Cardiol*. 2007;99(8):1146-1150.
61. Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation*. 2012;125(2):289-297.
62. Robbins IM, Hemnes AR, Pugh ME, et al. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. *Circ Heart Fail*. 2014;7(1):116-122.
63. Fox BD, Shimony A, Langleben D, et al. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. *Eur Respir J*. 2013;42(4):1083-1091.
64. Delgado JF, Conde E, Sánchez V, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. *Eur J Heart Fail*. 2005;7(6):1011-1016.
65. Kurdak SS, Namba Y, Fu Z, Kennedy B, Mathieu-Costello O, West JB. Effect of increased

duration of high perfusion pressure on stress failure of pulmonary capillaries. *Microvasc Res*. 1995;50(2):235-248.
66. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation*. 2011;124(2):164-174.
67. Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation*. 2007;116(14):1555-1562.
68. Redfield MM, Chen HH, Borlaug BA, et al; RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309(12):1268-1277.
69. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J*. 1997;134(1):44-54.
70. Packer M, McMurray JV, Krum H, et al; ENABLE Investigators and Committees. Long-Term Effect of Endothelin Receptor Antagonism With Bosentan on the Morbidity and Mortality of Patients With Severe Chronic Heart Failure. *JACC Heart Fail*. 2017,5(5):317-326.
71. Stasch JP, Pacher P, Evgenov OV. Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. *Circulation*. 2011;123(20):2263-2273.
72. Bonderman D, Ghio S, Felix SB, et al; Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: a phase IIb double-blind, randomized, placebo controlled, dose-ranging hemodynamic study. *Circulation*. 2013;128(5):502-511.
73. Bonderman D, Pretsch I, Steringer-Mascherbauer R, et al. Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized, double-blind, placebo controlled, single-dose study. *Chest*. 2014;146(5):1274-1285.