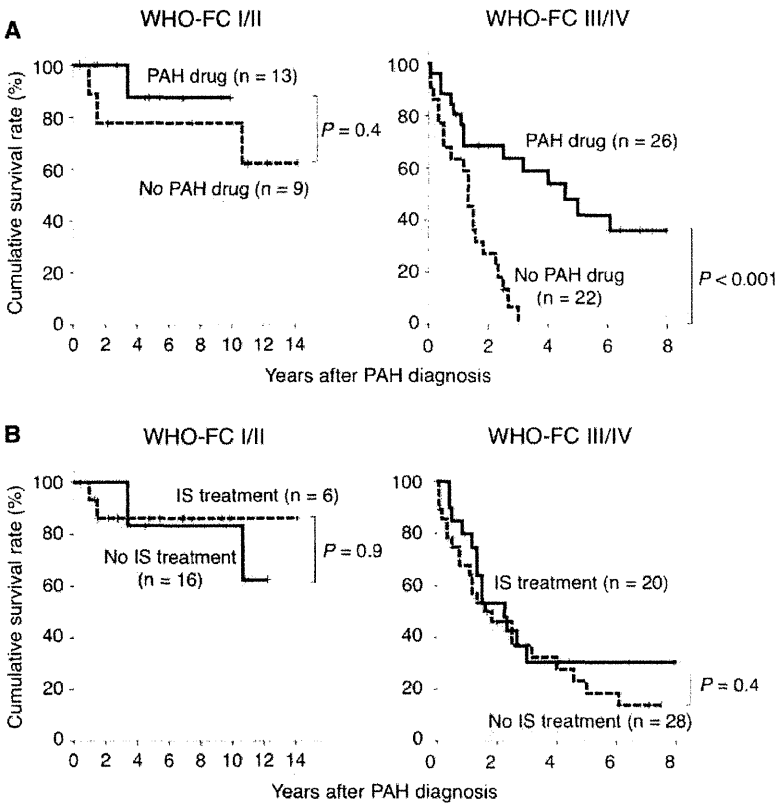
FIG. 3 Cumulative survival rates in 70 patients with PAH-CTD, stratified by treatment regimen.



Comparisons were made in patients with WHO-FC I/II and those with WHO-FC III/IV separately. (**A**) The cumulative survival rate was compared between patients who received at least one PAH drug and those who did not. (**B**) The cumulative survival rate was compared between patients who received immunosuppressive (IS) treatment and those who did not. Comparisons between two groups were made using the log-rank test.

expected by a recent campaign aimed to promote the PAH screening of asymptomatic patients with CTD but the recent group included more referral patients than the historical group. This may explain the differences in the baseline characteristics of the historical and recent groups: the haemodynamics were more severe and the frequency of MCTD lower in the recent group. Additionally, as in studies carried out in other east Asian countries [27–30], a small number of the patients in our cohort may have been subject to selection bias. Therefore, the subjects in our study might not reflect the composition of the general PAH-CTD patient population in Japan. Another limitation of this study is the lack of male patients in the study population, since a recent study demonstrated potential differences in baseline haemodynamic characteristics and outcomes between men and women with PAH [36].

In summary, the underlying CTDs and ANA profiles in Japanese patients with PAH-CTD were apparently different from those in the USA and Europe. Modern PAH treatment improves survival rates, but long-term outcomes are still unsatisfactory. Early detection of PAH is important for further improving survival rates but a screening strategy specific to Japanese CTD patients needs to be developed.

Rheumatology key messages

- High frequencies of MCTD/SLE and anti-U1RNP antibody are hallmarks of PAH-CTD in Japanese patients.
- The prognosis of Japanese patients with PAH-CTD has improved with modern treatment.
- WHO-FC at baseline is an independent prognostic factor in Japanese patients with PAH-CTD.

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References

1 Koh ET, Lee P, Gladman DD *et al.* Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. Br J Rheumatol 1996;35:989–93.

2 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;54:184–91.

3 Vegh J, Szodoray P, Kappelmayer J *et al.* Clinical and immunoserological characteristics of mixed connective tissue disease associated with pulmonary arterial hypertension. Scand J Immunol 2006;64:69–76.

4 Chung L, Liu J, Parsons L *et al.* Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. Chest 2010;138:1383–94.

5 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; 179:151–7.

6 Humbert M, Sitbon O, Chaouat A *et al.* Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023–30.

7 Ruiz-Cano MJ, Escribano P, Alonso R *et al.* Comparison of baseline characteristics and survival between patients with idiopathic and connective tissue disease-related pulmonary arterial hypertension. J Heart Lung Transplant 2009;28:621–7.

8 Steen V, Medsger TA Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. Arthritis Rheum 2003;48: 516–22.

9 Mukerjee D, 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;62:1088–93.

10 Launay D, Humbert M, Berezne A *et al.* Clinical characteristics and survival in systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease. Chest 2011;140:1016–24.

11 Hesselstrand R, Wildt M, Ekmehag B, Wuttge DM, Scheja A. Survival in patients with pulmonary arterial hypertension associated with systemic sclerosis from a Swedish single centre: prognosis still poor and prediction difficult. Scand J Rheumatol 2011;40:127–32.

12 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;60:569–77.

13 Kasukawa R, Nishimaki T, Takagi T *et al.* Pulmonary hypertension in connective tissue disease. Clinical analysis of sixty patients in multi-institutional study. Clin Rheumatol 1990;9:56–62.

14 Williams MH, Das C, Handler CE *et al.* Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. Heart 2006;92:926–32.

15 Hachulla E, Carpentier P, Gressin V *et al.* Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study. Rheumatology 2009;48:304–8.

16 Denton CP, Pope JE, Peter HH *et al.* Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. Ann Rheum Dis 2008;67:1222–8.

17 Badesch DB, Champion HC, Sanchez MA *et al.* Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;30:S55–66.

18 Denton CP, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. Ann Rheum Dis 2006;65:1336–40.

19 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40: 1725.

20 Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee: preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.

21 Kasukawa R, Tojo T, Miyawaki S. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp GC, eds. Mixed connective tissue disease and antinuclear antibodies. Amsterdam: Elsevier, 1987:41–7.

22 Vitali C, Bombardieri S, Jonsson R *et al.* Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. Ann Rheum Dis 2002;61:554–8.

23 Kuwana M, Kaburaki J, Okano Y, Tojo T, Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. Arthritis Rheum 1994;37:75–83.

24 Campo A, Mathai SC, Le Pavec J *et al.* Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. Am J Respir Crit Care Med 2010; 182:252–60.

25 Smolen JS, Steiner G. Mixed connective tissue disease: to be or not to be? Arthritis Rheum 1998;41:768–77.

26 Medsger TA. Natural history of systemic sclerosis and the assessment of disease activity, severity, functional status, and psychologic well-being. Rheum Dis Clin North Am 2003;29:255–73.

27 Miyamichi-Yamamoto S, Fukumoto Y, Sugimura K *et al.* Intensive immunosuppressive therapy improves pulmonary hemodynamics and long-term prognosis in patients with pulmonary arterial hypertension associated with connective tissue disease. Circ J 2011;75:2668–74.

28 Chen CH, Chen HA, Wang HP *et al.* Pulmonary arterial hypertension in autoimmune diseases: an analysis of 19 cases from a medical center in northern Taiwan. J Microbiol Immunol Infect 2006;39:162–8.

29 Zhang R, Dai LZ, Xie WP *et al.* Survival of Chinese patients with pulmonary arterial hypertension in the modern management era. Chest 2011;140:301–9.

30 Kim WU, Min JK, Lee SH, Park SH, Cho CS, Kim HY. Causes of death in Korean patients with systemic lupus erythematosus: a single center retrospective study. Clin Exp Rheumatol 1999;17:539–45.

31 Lau EM, Manes A, Celermajer DS, Galiè N. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. Eur Heart J 2011;32:2489–98.

32 Avouc 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;37:2290–8.

33 Hachulla E, Gressin V, Guillevin L *et al.* Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005;52:3792–800.

34 Sanchez O, Stibon O, Jais X, Simonneau G, Humbert M. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. Chest 2006;130:182–9.

35 Kato M, Kataoka H, Odani T *et al.* The short-term role of corticosteroid therapy for pulmonary arterial hypertension associated with connective tissue diseases: report of five cases and a literature review. Lupus 2011;20:1047–56.

36 Shapiro S, Traiger GL, Turner M, McGoon MD, Wason P, Barst RJ. Sex differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension management. Chest 2012;141:363–73.

Leading Article

Combined Interstitial Lung Disease and Pulmonary Hypertension in Systemic Sclerosis: Pathophysiology and Management

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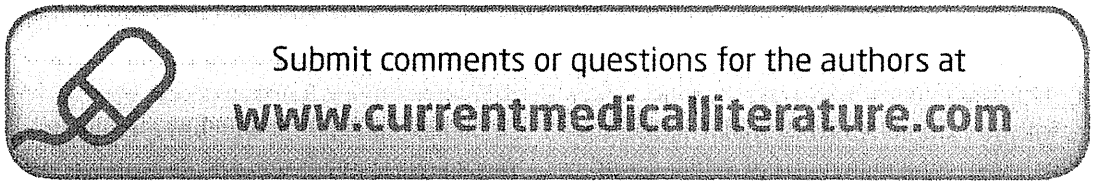


Systemic sclerosis (SSc), also known as scleroderma, is a connective tissue disease (CTD) characterized by excessive fibrosis, microvasculopathy, and autoimmunity. Typical histological changes are found in multiple organs, including the skin, gastrointestinal tract, lungs, heart, and kidneys. Lung involvement is a major cause of morbidity and mortality in SSc. In fact, University of Pittsburgh (Pittsburgh, PA, USA) database records of SSc-related mortality show interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) as the two major causes of death [1]. Thus, to improve SSc patient survival, it is imperative to suppress the progression of ILD and PAH. Currently, treatment for SSc-associated ILD is limited to immunosuppressive agents. A recent randomized placebo-controlled trial (the Scleroderma Lung Study) reported that oral cyclophosphamide provides a modest but significant benefit in terms of lung function and health-related quality of life (QoL) in SSc patients with active ILD [2]. Molecularly targeted drugs for PAH can greatly benefit patients with SSc-associated PAH, improving symptoms, QoL, hemodynamics, and survival in comparison with historical controls [3]. However, it is still unclear whether these new treatments will improve long-term prognosis [4].

Clinically, a significant proportion of patients with SSc have co-occurring ILD and pulmonary hypertension (PH) [5], and these cases are the most difficult to manage. The prognosis for these patients is worse than for patients with ILD or PAH alone [6–8]. The exact pathophysiology of coexisting ILD and PH in SSc patients is uncertain; these two conditions may interact synergistically to deteriorate cardiopulmonary function. In this review, we will summarize current information on the pathophysiology and management of SSc with combined ILD and PH.

Pathophysiology

PH is a heterogeneous condition characterized by elevated PA pressure. The clinical classifications of PH were updated at the World PH Symposium held in 2008

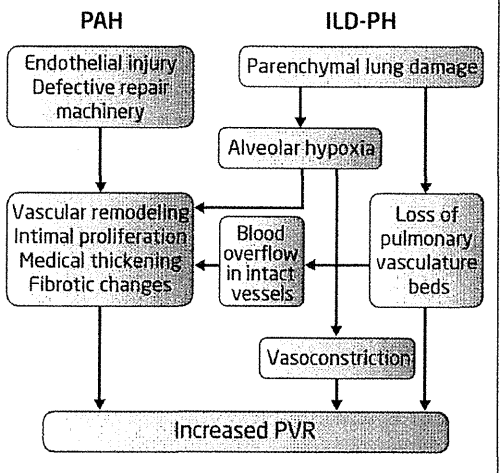
[9]. All forms of PH can occur in patients with SSc, including PAH, pulmonary veno-occlusive disease (PVOD), PH owing to left heart disease (LHD), PH owing to lung diseases and/or hypoxia, and chronic thromboembolic PH. In a recent European cohort of SSc patients with PH, the frequencies of PAH, PVOD, PH-LHD, and PH-ILD were 51%, 2%, 20%, and 27%, respectively [10]. Clearly, the underlying disease processes of PH in SSc are heterogeneous, and it is important to note that PH owing to myocardial dysfunction or ILD is fairly common in SSc [10,11]. In addition, many SSc patients with PH show mixed histological features of PAH and PVOD at autopsy [12], and high-resolution computed tomography (HRCT) findings suggestive of PVOD are associated with a worse prognosis in SSc patients with a diagnosis of PAH [13]. Furthermore, subclinical diastolic myocardial dysfunction, which may contribute to passive PH, is fairly common in SSc patients [14]. Therefore, it is likely that many SSc patients with PH have two or more conditions that together contribute to elevation of PA pressure (PAP).

The clinical classification of PH cases is based on the primary causative underlying condition, but in SSc patients it is often difficult to identify which mechanism plays the primary role. Where radiological evidence indicates that ILD and PH coexist, it is practically impossible to discriminate PH-ILD from co-occurring PAH and ILD. Previous studies evaluating SSc patients with PAH have used a variety of criteria to exclude PH-ILD, including percent total lung capacity (TLC) <80% [15] or <70% [16], and percent forced vital capacity (FVC) <60% [17] or <70% [18]. Other studies examining the impact of coexisting ILD on the survival of SSc patients with PH have included subjects with PH whose HRCT results provided radiological evidence of ILD [6,7,8,19]. Thus, the inconsistent inclusion and exclusion criteria used in the current literature make it difficult to understand the pathophysiology, prevalence, and natural history of combined ILD and PH in SSc patients.

Two types of pathogenic process, including PAH and PH-ILD, contribute to increased PAP in SSc patients with ILD (**Figure 1**). PAH primarily affects the distal PA and promotes vascular remodeling. The pathogenic lesions are characterized by pulmonary vascular remodeling consisting of medial hypertrophy and intimal proliferative and fibrotic changes [20]. In contrast, the predominant cause of PH-ILD is alveolar hypoxia owing to parenchymal lung disease [21]. Hypoxia induces vasoconstriction of the pulmonary arterioles and resultant elevation of pulmonary vascular resistance (PVR). This response is often reversible, but chronic hypoxic vasoconstriction may eventually lead to pulmonary vascular remodeling, as observed in PAH. The loss of capillary surface area as a result of the destruction of lung parenchyma may also contribute to increased PVR. Again, this mechanism promotes vascular remodeling of the intact pulmonary vasculature by increasing shear stress owing to blood overflow. These processes together increase PVR.

Recent observational studies on nailfold capillary changes in SSc patients suggest that structural vascular abnormalities occur very early in disease progression, preceding fibrotic changes [22]. Endothelial injury and defective vascular repair machinery have been proposed as the primary event leading to SSc, followed by an influx of circulating inflammatory cells and progenitors accompanied by the upregulation of a series of pro-fibrotic growth factors, such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF) [23]. Therefore, it is important to be aware that remodeling of the peripheral vasculature, including the PAs, is found in all patients with a clinical diagnosis of SSc. In particular, this process occurs early in the course of the disease, before ILD progresses to cause hypoxia or a significant loss of pulmonary vasculature. Taken together, SSc patients with combined ILD and PH have the PA pathophysiology of both PAH and PH-ILD, but the degree to which these two conditions contribute differs among patients.

Figure 1. Pathogenic mechanisms contributing to elevation of pulmonary arterial pressure in systemic sclerosis patients with combined PH and ILD. Two types of pathogenic process, PAH and PH-ILD, synergistically promote increased PVR.



ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; PVR: pulmonary vascular resistance.

Proportion of PH in SSc patients with ILD

Chang and coworkers examined the frequencies of ILD and PH in 619 patients with SSc [5]. ILD, defined as a TLC <80%, was present in 251 patients (41%), while PH, determined by Doppler echocardiography estimation as a systolic PAP (PASP) >35 mmHg, was detected in 231 patients (37%). A total of 112 patients (18%) had both ILD and PH; thus, the proportion of PH in SSc patients with ILD was 44%. Trad et al. reported ILD in 52 (60%) of 86 patients with diffuse cutaneous SSc (dcSSc); 18 patients (35%) were found to have concomitant PH, based on Doppler echo [19]. However, the percentages in these studies apparently over-represent the incidence of PH in SSc patients with ILD, because Doppler echo can lead to overestimation of PASP [24]. To date, no study has been conducted to assess the proportion of PH confirmed by right heart catheterization (RHC) in patients with SSc and ILD. Nevertheless, the prevalence of PH in SSc patients with ILD appears to be extremely high compared with the prevalence of <5% in patients with primary parenchymal lung diseases, such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) [25]. This supports the theory that PH in SSc patients with ILD results not only from PH-ILD, but also from the primary vascular remodeling observed in PAH.

In patients with SSc, the prevalence of PH was reported to be in the range of 7–12% when PH was detected by Doppler echo screening, followed by confirmatory RHC [10]. Several cohort studies have evaluated the prevalence of PH-ILD in SSc patients with RHC-confirmed pre-capillary PH, using their own definitions based on pulmonary function tests (PFTs) [6,7,19]. The prevalence was strikingly similar in these reports, ranging from 18% to 21%.

Clinical characteristics

Risk factors for developing PAH in SSc include limited cutaneous SSc, long disease duration from the onset of Raynaud's phenomenon (>8 years), anticentromere antibodies (ACA), anti-nuclear antibodies, and extensive telangiectasia [26]. In contrast, ILD is associated with dcSSc, anti-topoisomerase I antibodies, and the absence of ACA [15]. Characteristics of coexisting ILD and PH include male gender with a history of smoking, dcSSc, and a low percentage of ACA [8], which are consistent with ILD risk factors and apparently different from PAH risk factors.

Combined pulmonary fibrosis and emphysema (CPFE) syndrome has been proposed as a distinct subset of ILD, with imaging features including centrilobular and/or paraseptal emphysema, and diffuse infiltrative opacities suggestive of pulmonary fibrosis predominating in the lower lobes [27]. CPFE has distinct clinical features characterized by a history of smoking, severe dyspnea, and unexpectedly subnormal spirometry measurements contrasting with severely impaired gas exchange; it carries an increased risk of developing PH [28,29]. Recently, Cottin et al. reported that CPFE occurs in patients with CTDs, including SSc, and is present in 7% of the entire ILD population [30]. Of particular interest, RHC-confirmed PH was detected in half of

the SSc patients with CPFE, indicating a strong correlation between CPFE and PH.

Hemodynamics

Patients with PH and advanced parenchymal disease such as COPD or IPF often have only mildly impaired hemodynamic parameters. Cardiac output is usually still within the normal range, and PVR is slightly or moderately increased [31]. The increase in mean PAP (mPAP) is also generally modest, ranging 25–35 mmHg [32]. However, some patients have prominently elevated PAP of >35 mmHg. These patients, particularly those with relatively mild pulmonary function impairment or ILD extent on chest HRCT, are considered to have "out of proportion" PH, which is supposed to indicate additional conditions contributing to increased PAP, such as pulmonary vascular remodeling. The prevalence of out-of-proportion PH in SSc patients with ILD should be higher than in patients with COPD or IPF, but there are few data on this issue because different definitions have been used to select patients with combined ILD and PH in the studies published to date [33]. Interestingly, survival rates in SSc patients with combined ILD and PH are similar among those with mild and moderate-to-severe increases in PAP, suggesting that PAP is not prognostically significant [8].

Prognosis

The median life expectancy of SSc patients with PAH is approximately 1 year if PAH remains untreated [34]. Treatment has evolved considerably with the recent development of PAH drugs [35]. In contrast, the median survival of SSc patients with ILD is 5–8 years when not treated with cyclophosphamide [36]. **Table 1** summarizes the short-term survival rates of SSc patients with combined ILD and PH, although the definition of ILD differed among these studies. The majority of subjects were treated with one or more PAH drugs. These studies consistently showed worse survival rates for patients with combined ILD and PH than for those with PAH alone. The 3-year survival rates were disappointingly low, ranging from 28% to 47%. A multivariate analysis of all patients with PH found ILD to be the independent parameter associated with the worst survival rate [6]. The risk of death increased five-fold for SSc patients with combined ILD and PH compared with those with PAH alone.

Prognostic factors determined in a multivariate analysis in SSc patients with combined ILD and PH are listed in **Table 2**. Launay et al. found that pericardial effusion and lowered diffusing capacity of the lung for carbon monoxide (DLCO) were independent factors predictive of poor survival in SSc patients with combined ILD and PH [8]. Another study found deterioration of oxygenation during follow-up and reduced glomerular filtration rate to be independent predictors of mortality [37]. Interestingly, none of the hemodynamic parameters was found to be a prognostic parameter in this group of patients.

Screening and diagnosis

The general recommendation for SSc patients is to be screened annually for PAH, even in the absence of symptoms [26], since PAH is a typical late complication of SSc [26]. On the other hand, Hachulla et al. recently reported that approximately half of their SSc patients who developed PAH had an early onset of the complication [38]. Current guidelines recommend that patients with a high risk of developing PH, such as those with SSc, be screened with transthoracic echo irrespective of the presence or absence of ILD [39]. Patients with echo findings suggestive of PH, such as right ventricle enlargement, abnormal intraventricular septum configuration, and increased tricuspid regurgitation peak velocity, should undergo RHC, the gold standard for confirming a PH diagnosis.

Echo, the most commonly used screening tool, is often unreliable, especially in the presence of parenchymal lung diseases such as COPD [24]. In such patients, the chest wall configuration – especially if there is air trapping or a deviated cardiac orientation – may affect the results of the echo. In addition, increased tricuspid regurgitation velocity was

Table 1. Short-term survival rates in systemic sclerosis patients with RHC-confirmed PH in the presence or absence of ILD. Definition of PH is based on RHC (mean PA pressure ≥25 mmHg, PA occlusion pressure <15 mmHg).

Study [Ref]	Participants (n)			Definition of ILD	Survival rates	
	Total	Without ILD	With ILD		Without ILD (%)	With ILD (%)
Mathai et al., 2009 [6]	59	39	20	TLC <60% or TLC 60–70% plus "severe" ILD on HRCT	1 year: 87 2 years: 79 3 years: 64	1 year: 82 2 years: 46 3 years: 39
Condliffe et al., 2009 [7]	315	259	56	Predicted forced vital capacity <60%	1 year: 78 2 years: 58 3 years: 47	1 year: NA 2 years: NA 3 years: 28
Launay et al., 2011 [8]	97	50	47	ILD on HRCT	3 years: 71	3 years: 47

HRCT: high-resolution computed tomography; ILD: interstitial lung disease; NA: data not available; PA: pulmonary artery; PH: pulmonary hypertension; RHC: right heart catheterization; TLC: predicted total lung capacity.

detected by echo in only 24–77% of patients in whom a pressure gradient was detected by RHC [40–42]. A recent study evaluating the relationship between echo and RHC data in COPD patients found the positive and negative predictive values of echo results to be 68% and 67%, respectively [43]. Therefore, it is important to understand the diagnostic limitations of echo.

The PFT is also useful for screening SSc patients for PAH. Steen et al. reported that 11% of 815 patients with SSc had "isolated" DLCO reduction – that is, reduced DLCO in spite of normal FVC, without radiological evidence of ILD – and that this finding was associated with PAH [44]. In the presence of advanced ILD, a disproportionate decline in DLCO, which is expressed by a ratio of FVC to DLCO >1.4, is useful for identifying patients with combined ILD and PH. Another study reported that the sensitivity and specificity of the FVC/DLCO ratio for detecting PH in SSc patients were 71% and 72%, respectively, when the cutoff was set at 2.0 [45]. However, the FVC/DLCO ratio was relatively low in SSc patients with combined ILD and PH compared with those with PAH alone [6]. This finding was confirmed by Launay et al., indicating limited utility of the FVC/DLCO ratio for PH screening in SSc patients with ILD [8]. Instead, this group of investigators found reduced partial pressure of oxygen in the arterial blood to be an independent indicator of concomitant ILD and PH, whereas severe dyspnea was a unique indicator for PAH without ILD [46].

The plasma level of B-type natriuretic peptide (BNP) or its precursor, N-terminal pro-BNP (NT-proBNP), is a useful marker for detecting PAH in patients with SSc [47,48]. In patients with parenchymal lung disease, elevated BNP concentrations have been found to have a sensitivity of 85% and a specificity of 88% in identifying significant PH and predicting mortality [49]. BNP is a risk factor for death, independent of lung function impairment or hypoxemia. However, left ventricular end-systolic wall stress appears to be the key mechanical stimulus for releasing NT-proBNP [50], indicating that BNP is not always reliable, especially in the presence of LHD.

RHC is the gold standard for diagnosing PH. RHC can be used in SSc patients with ILD to achieve the following:

- To confirm or exclude a diagnosis of PH.
- To classify "out of proportion" PH.
- To assess severity by examining such hemodynamics as cardiac output and PVR.
- To evaluate concomitant myocardial involvement by measuring pulmonary capillary wedge pressure.

Therefore, SSc patients with ILD who have dyspnea and hypoxemia disproportionate to PFT and HRCT findings, or who have signs of

Table 2. Prognostic factors in patients with combined interstitial lung disease and PH, determined by multivariate analysis.

Study [Ref]	Statistically significant prognostic factors	Factors not associated with prognosis
Launay et al., 2011 [8]	DLCO Pericardial effusion	Sex Age Age at SSc diagnosis SSc duration at PH diagnosis Anticentromere antibody Anti-topoisomerase I antibody Partial pressure of oxygen in arterial blood WHO functional class 6MWD RHC parameters (RAP, mPAP, CI, PVR, stroke volume, stroke volume index, right ventricle stroke work index) Heart rate PFT parameters (TLC, FVC, FEV1, FVC/DLCO)
Le Pavec et al., 2011 [37]	Reduced glomerular filtration rate Worsening oxygenation	Age Sex SSc duration prior to pulmonary arterial hypertension diagnosis Limited or diffuse Oxygen usage at baseline WHO functional class 6MWD Heart rate Mean systolic blood pressure RHC parameters (RAP, mPAP, CI, PVR) PFT parameters (FEV1, FVC, TLC, DLCO)

6MWD: 6-min walk distance; CI: cardiac index; DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; mPAP: mean pulmonary arterial pressure; PFT: pulmonary function test; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; RAP: right atrial pressure; RHC: right heart catheterization; SSc: systemic sclerosis; TLC: total lung capacity; WHO: World Health Organization.

right-sided heart failure, should undergo RHC irrespective of PH screening results.

After PH is confirmed by RHC, it is necessary to classify patients with combined ILD and PH into at least three groups based on the degree of functional impairment. In the case of mild ILD without restrictive respiratory impairment, PH is likely to be due to primary PA remodeling, consistent with PAH. On the other hand, it is difficult to discriminate the co-occurrence of ILD and PAH from PH-ILD alone in the presence of clinically relevant ILD, which may correspond to extensive disease, as proposed by Goh et al. [51]. There is no consensus on criteria for discriminating patients with and without concomitant PAH. In these circumstances, subgrouping of out-of-proportion PH is potentially useful for selecting patients with coexistent PH-ILD and PAH. Definition of out-of-proportion PH is still a matter of debate, but preliminary criteria were proposed at the Cologne Consensus Conference in 2011 [31]. Specifically, classification into out-of-proportion PH requires at least two of three criteria: mPAP >35 mmHg, mPAP >25 mmHg with limited cardiac output (cardiac index <2.0 l/min/m^2), and PVR >6 WU. These tentative criteria may be used as a guide for classification of SSc patients with combined ILD and PH, but the clinical decision should be made on a case-by-case basis.

Management

Currently, there is no treatment proven to improve survival in SSc patients with combined ILD and PH. Since this group of patients has the worst prognosis of all patients with SSc, all potentially effective treatment options available must be considered.

Treatment for ILD

Oral cyclophosphamide is widely accepted for the treatment of SSc-associated ILD, based on the results of a randomized

placebo-controlled trial [2]; however, that study excluded patients with apparent PH. Oral cyclophosphamide has a beneficial but modest effect on lung function, and in one study this small effect was no longer apparent 1 year after cyclophosphamide treatment ended [52]. Two independent meta-analyses failed to demonstrate any clinically significant improvement in pulmonary function in SSc patients treated with cyclophosphamide [53,54]. On the other hand, another study found a clinical response to cyclophosphamide in a subset of ILD patients, with the predictors of clinical benefit including FVC <70% and moderate pulmonary fibrosis on HRCT [55]. Therefore, the indication for cyclophosphamide should be restricted to patients with these potential predictors.

Alternative regimens for treating SSc-associated ILD include endothelin receptor antagonists (ERAs), such as bosentan. A randomized, placebo-controlled trial was conducted to investigate the potential efficacy of bosentan for SSc-associated ILD – BUILD-2 (Bosentan in ILD in SSc 2) – but failed to show improvements in lung function or 6-min walk distance (6MWD) with bosentan [56]. In addition, new onset of PH during bosentan therapy has been reported in SSc patients with advanced ILD [57]. Recently, the Committee for Medical Products for Human Use of the European Medicines Agency added IPF with or without PH to a list of contraindications for ambrisentan, based on the results of clinical trials [58]. Detailed information has yet to be provided, but, meanwhile, caution is warranted when considering ambrisentan in SSc patients with clinically relevant ILD.

Oxygen supplementation

In general, long-term oxygenation therapy is beneficial for patients who have both ILD and PH [59]. The rationale for providing oxygen is that alveolar hypoxia is the predominant mechanism for the development of PH in patients with ILD, but there is no evidence showing that oxygen therapy stabilizes structural PA remodeling [60]. In PAH treatment algorithms, patients are advised to maintain an oxygen saturation >92% using long-term oxygenation therapy [60]. In addition, European Society of Cardiology (ESC) and European Respiratory Society guidelines advise patients to use low-dose oxygen therapy to achieve an arterial blood oxygen pressure of >8 kPa (60 mmHg) for ≥15 h/day [61]. Non-invasive positive pressure ventilation is a potential option for patients with combined ILD and PH and with severely impaired gas exchange [62].

PAH drugs

The current drug treatment options for PAH include prostanoids, phosphodiesterase-5 (PDE-5) inhibitors, and ERAs. These drugs are of clinical benefit for SSc patients with PAH [35,63], but the effects in SSc patients with combined ILD and PH remain controversial [35,64–66]. In a retrospective observational study of 19 patients with PH and moderate or severe ILD, epoprostenol or bosentan produced short-term functional benefits that had disappeared at 1 year of follow-up [66]. Le Pavec and colleagues retrospectively examined clinical responses to PAH drugs in 70 patients with SSc and combined ILD and PH [37]. Most patients were initially treated with an ERA or a PDE-5 inhibitor, and many ultimately received a second or third PAH agent. In this patient population, no significant change was observed in World Health Organization functional class, 6MWD, or any hemodynamic parameter after PAH drug therapy. The multivariate model did not select the use of any PAH drug as a factor associated with improved survival.

In the presence of advanced parenchymal lung disease such as ILD, PAH drugs can potentially increase the ventilation/perfusion mismatch, thereby worsening oxygenation [67]. Theoretically, blood flow in the pulmonary circulation is directed to well-ventilated areas to ensure optimized gas exchange, with minimal blood flow being directed through areas with little or no ventilation owing to hypoxic vasoconstriction. When non-selective vasodilators are used in

the setting of advanced ILD, vasodilation is induced in poorly ventilated areas of the lung, resulting in venous admixture and deterioration of gas exchange. In particular, intravenous prostanoids often cause this unfavorable effect [68]. As a result, intravenous epoprostenol is not recommended for patients with advanced ILD. By contrast, inhaled prostanoids have been shown to reduce PAP and increase cardiac output in patients with combined PH and ILD, without causing a significant drop in systemic artery pressure or increase in ventilation/perfusion mismatch [69]. PDE-5 inhibitors may preferentially improve blood flow to well-ventilated regions of the lung in patients with advanced ILD, and therefore should not exacerbate and may even improve the ventilation/circulation mismatch. This favorable effect of sildenafil was confirmed in a randomized, controlled, open-label trial involving 16 patients with combined ILD and PH in which patients were assigned to treatment with either epoprostenol or sildenafil [68]. In a recent double-blind, randomized, placebo-controlled trial in patients with IPF, sildenafil failed to increase the 6MWD but significantly improved secondary outcomes, including arterial oxygenation, DLCO, degree of dyspnea, and QoL [70].

Again, there is no clear evidence showing the effectiveness of PAH drugs for SSc patients with combined ILD and PH. PAH drugs may be used with great caution when PAH pathophysiology is likely to be contributing to increased PVR, such as PH with mild or subtle ILD and out-of-proportion PH. In this case, PDE-5 inhibitors and inhaled prostanoids, which are unlikely to increase ventilation/perfusion mismatch, are reasonable options. Bosentan may be used, but the use of ambrisentan should be avoided.

Tyrosine kinase inhibitors

Another option for treating combined ILD and PH is the use of tyrosine kinase inhibitors (TKIs) such as imatinib or nilotinib, since this class of drugs is potentially effective for both ILD and PH. TKIs suppress intracellular signals involved in vascular remodeling and excessive fibrosis, such as TGF-β, PDGF, and c-kit [71]. In animal models, imatinib has been found to be effective for preventing monocrotaline-induced PH [72] and bleomycin-induced lung fibrosis [73]. Imatinib also has potent pulmonary vasodilatory activity, mediated through vascular smooth muscle relaxation [74]. In patients with severe idiopathic PAH (IPAH), adding imatinib to PAH drug therapy improves pulmonary hemodynamics and functional capacity [75–77]. A recent clinical trial evaluating the efficacy of imatinib in patients with PAH failed to meet the primary endpoint of improvement in 6MWD; however, many secondary endpoints, including pulmonary hemodynamics such as PVR and cardiac output, improved significantly [78]. On the other hand, another clinical trial found that imatinib treatment of patients with IPF did not significantly improve survival or lung function compared with placebo, but imatinib-treated patients showed significantly improved oxygenation at 48 weeks, and these positive effects were sustained for 96 weeks [79]. Current evidence does not support imatinib as an effective treatment for SSc patients with combined ILD and PH, but TKIs may offer a potential treatment strategy for this serious condition.

At least three clinical trials of imatinib have been conducted in patients with early dcSSc. Two pilot open-label studies showed a trend toward improvement of skin thickening and FVC [80,81], but no efficacy was found in a randomized double-blinded placebo-controlled trial [82]. Patients with PAH or advanced ILD were excluded from these trials, but it should be noted that many patients dropped out because of adverse events, including gastrointestinal symptoms and peripheral edema, and one trial was even terminated because of safety concerns. The dosage of imatinib is one of the factors associated with the occurrence of adverse events, but in general safety precludes clinicians from using imatinib for SSc patients who have multiple organ involvement.

Lung transplantation

Lung transplantation is a viable and potentially life-saving approach for managing SSc patients with end-stage ILD, PAH, or both, and is still a mainstay of treatment for these devastating conditions. However, SSc is considered a poor candidate for transplantation because multiple comorbidities, including gastroesophageal reflux, renal impairment, and skin fibrosis, increase the risk of procedure-related death [83]. Despite strict inclusion and exclusion criteria being used to select SSc patients without those risk factors in one study, the cumulative survival rate at 6 months post-transplantation was still 69% in the SSc group, compared with 80% in the IPF group and 79% in the IPAH group [84]. In a recent single-center study that evaluated the prognosis of bilateral lung transplantation, the 1-year all-cause mortality rate was 6.6% in patients with SSc and 13.6% in those with IPF [85].

Conclusions

Among SSc patients, those with combined ILD and PH have the worst survival rates, and progress remains poor despite recent therapeutic advances. Furthermore, the underlying pathophysiology of combined ILD and PH in SSc patients remains unclear, although it is likely that multiple mechanisms are involved. The limited effectiveness of current treatments and the devastating nature of this condition continue to drive the search for novel therapeutic targets.

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References

1. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007;66:940-4.
2. Tashkin DP, Elashoff R, Clements PJ et al.; Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006;354:2655-66.
3. Williams MH, Das C, Handler CE et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. *Heart* 2006;92:926-32.
4. Le Pavec J, Humbert M, Mouthon L et al. Systemic sclerosis-associated pulmonary arterial hypertension. *Am J Resipir Crit Care Med* 2010;181:1285-93.
5. Chang B, Wigley FM, White B et al. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. *J Rheumatol* 2003;30:2398-405.
6. Mathai SC, Hammers LK, Champion HC et al. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. *Arthritis Rheum* 2009;60:569-77.
7. 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;179:151-7.
8. Launay D, Humbert M, Berezne A et al. Clinical characteristics and survival in systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease. *Chest* 2011;140:1016-24.
9. Simonneau G, Robbins IM, Beghetti M et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54(1 Suppl):43-54.
10. Avouac J, Airò P, Meune C et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *J Rheumatol* 2010;37:2290-8.
11. Hinchcliff M, Fisher A, Schiopu E et al.; PHAROS Investigators. Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): baseline characteristics and description of study population. *J Rheumatol* 2011;38:2172-9.
12. Overbeek MJ, Vonk MC, Boonstra A et al. Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. *Eur Respir J* 2009;34:371-9.
13. Günther S, Jaïs X, Maitre S et al. Computed tomography findings of pulmonary venoocclusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. *Arthritis Rheum* 2012;64:2995-3005.
14. Kahan A, Coghlan G, McLaughlin V. Cardiac complications of systemic sclerosis. *Rheumatology (Oxford)* 2009;48 (Suppl 3):45-8.
15. Phung S, Strange G, Chung LP et al. Prevalence of pulmonary arterial hypertension in an Australian scleroderma population: screening allows for earlier diagnosis. *Intern Med J* 2009;39:682-91.
16. Vonk MC, Broers B, Heijdra YF et al. Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. *Ann Rheum Dis* 2009;68:961-5.
17. Hachulla E, Gressin V, Guillevin L et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nation wide prospective multicentre study. *Arthritis Rheum* 2005;52:3792-800.
18. Mukerjee D, St George D, Knight C et al. Echocardiography and pulmonary function as screening tests for pulmonary hypertension in systemic sclerosis. *Rheumatology (Oxford)* 2004;43:461-6.
19. 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;54:184-91.
20. Tuder RM. Pathology of pulmonary arterial hypertension. *Semin Respir Crit Care Med* 2009;30:376-85.
21. Farkas L, Kolb M. Pulmonary microcirculation in interstitial lung disease. *Proc Am Thorac Soc* 2011;8:516-21.
22. Herrick AL, Cutolo M. Clinical implications from capillaroscopic analysis in patients with Raynaud's phenomenon and systemic sclerosis. *Arthritis Rheum* 2010;62:2595-604.
23. Orr R, Smith LJ, Cuttica MJ. Pulmonary hypertension in advanced chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2012;18:138-43.
24. 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;167:735-40.
25. Chaouat A, Bugnet AS, Kadaoui N et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:189-94.

26. Fischer A, Bull TM, Steen VD. Practical approach to screening for scleroderma-associated pulmonary arterial hypertension. *Arthritis Care Res (Hoboken)* 2012;64:303-10.
27. Wiggins J, Strickland B, Turner-Warwick M. Combined cryptogenic fibrosing alveolitis and emphysema: value of high resolution computed tomography in assessment. *Respir Med* 1990;84:365-9.
28. Jankowich MD, Polsky M, Klein M et al. Heterogeneity in combined pulmonary fibrosis and emphysema. *Respiration* 2008;75:411-7.
29. Cottin V, Nunes H, Brillet PY et al.; Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires (GERM O P). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. *Eur Respir J* 2005;26:586-93.
30. Cottin V, Nunes H, Mouthon L et al.; Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires. Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. *Arthritis Rheum* 2011;63:295-304.
31. Hoeper MM, Andreas S, Bastian A et al. Pulmonary hypertension due to chronic lung disease: updated Recommendations of the Cologne Consensus Conference 2011. *Int J Cardiol* 2011;154(Suppl 1):45-53.
32. Weitzenblum E, Hirth C, Ducolone A et al. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 1981;36:752-8.
33. Kawut SM, Taichman DB, Archer-Chicko CL et al. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003;123:344-50.
34. Koh ET, Lee P, Gladman DD et al. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. *Br J Rheumatol* 1996;35:989-93.
35. Denton CP, Pope JE, Peter HH et al.; Tracleer Use in PAH associated with Scleroderma and Connective Tissue Diseases (TRUST) Investigators. Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. *Ann Rheum Dis* 2008;67:1222-8.
36. Altman RD, Medsger TA Jr, Bloch DA et al. Predictors of survival in systemic sclerosis (scleroderma). *Arthritis Rheum* 1991;34:403-13.
37. 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;63:2456-64.
38. Haculla E, Launay D, Mouthon L et al.; French PAH-SSc Network. Is pulmonary arterial hypertension really a late complication of systemic sclerosis? *Chest* 2009;136:1211-9.
39. McGoon M, Gutterman D, Steen V et al.; American College of Chest Physicians. Screening, early detection and diagnosis of pulmonary artery hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126(1 Suppl):14-34.
40. Tramarin R, Torbicki A, Machandise B et al.; Working Group on Noninvasive Evaluation of Pulmonary Artery Pressure. Doppler echocardiographic evaluation of pulmonary artery pressure in chronic obstructive pulmonary disease. A European multicentre study. *Eur Heart J* 1991;12:103-11.
41. Torbicki A, Skwarski K, Hawrylkiewicz I et al. Attempts at measuring pulmonary arterial pressure by means of Doppler echocardiography in patients with chronic lung disease. *Eur Respir J* 1989;2:856-60.
42. Laaban JP, Diebold B, Zelinski R et al. Noninvasive estimation of systolic pulmonary artery pressure using Doppler echocardiography in patients with chronic obstructive pulmonary disease. *Chest* 1989;96:1258-62.
43. Fisher MR, Cliner GJ, Fishman AP et al.; NETT Research Group. Estimating pulmonary artery pressures by echocardiography in patients with emphysema. *Eur Respir J* 2007;30:914-21.
44. Steen VD, Graham G, Conte C et al. Isolated diffusing capacity reduction in systemic sclerosis. *Arthritis Rheum* 1992;35:765-70.
45. Hsu VM, Moreyra AE, Wilson AC et al. Assessment of pulmonary arterial hypertension in patients with systemic sclerosis: comparison of noninvasive tests with results of right-heart catheterization. *J Rheumatol* 2008;35:458-65.
46. Launay D, Mouthon L, Haculla E et al. Prevalence and characteristics of moderate to severe pulmonary hypertension in systemic sclerosis with and without interstitial lung disease. *J Rheumatol* 2007;34:1005-11.
47. Leuchte HH, El Nounou M, Tuerpe JC et al. N-terminal pro-brain natriuretic peptide and renal insufficiency as a predictors of mortality in pulmonary hypertension. *Chest* 2007;131:402-9.
48. Williams MH, Handler CE, Akram R et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. *Eur Heart J* 2006;27:1485-94.
49. Leuchte HH, Baumgartner RA, Nounou ME et al. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir Crit Care Med* 2006;173:744-50.
50. Maeder MT, Mariani JA, Kaye DM. Hemodynamic determinants of myocardial B-type natriuretic peptide release: relative contributions of systolic and diastolic wall stress. *Hypertension* 2010;56:682-9.
51. Goh NS, Desai SR, Veeraraghavan S et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008;177:1248-54.
52. Tashkin DP, Elashoff R, Clements PJ et al.; Scleroderma Lung Study Research Group. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med* 2007;176:1026-34.
53. Nannini C, West CP, Erwin PJ et al. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. *Arthritis Res Ther* 2008;10:R124.
54. Broad K, Pope JE. The efficacy of treatment for systemic sclerosis interstitial lung disease: results from a meta-analysis. *Med Sci Monit* 2010;16:RA187-90.
55. Au K, Khanna D, Clements PJ et al. Current concepts in disease-modifying therapy for systemic sclerosis-associated interstitial lung disease: lessons from clinical trials. *Curr Rheumatol Rep* 2009;11:111-9.
56. 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;62:2101-8.
57. Furuya Y, Kuwana M. Effect of bosentan on systemic sclerosis-associated interstitial lung disease ineligible for cyclophosphamide therapy: a prospective open-label study. *J Rheumatol* 2011;38:2186-92.
58. Committee for Medicinal Products for Human Use (CHMP). Summary of opinion (post authorisation): Volibris (ambrisentan). Available at www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000839/WC500129075.pdf
59. Hoeper MM, Barberà JA, Channick RN et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *J Am Coll Cardiol* 2009;54(1 Suppl):85-96.
60. Weitzenblum E, Sautegeau A, Ehrhart M et al. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1985;131:493-8.
61. Galiè N, Hoeper MM, Humbert M; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the 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 the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493-537.
62. Moriyama K, Sugiyama S, Uzawa K et al. Noninvasive positive pressure ventilation against reperfusion pulmonary edema following percutaneous transluminal pulmonary angioplasty. *Case Rep Anesthesiol* 2011;2011:204538.
63. Rubin LJ, Badesch DB, Fleming TR et al.; SUPER-2 Study Group. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. *Chest* 2011;140:1274-83.
64. 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;49:490-500.
65. Mittoo S, Jacob T, Craig A et al. Treatment of pulmonary hypertension in patients with connective tissue disease and interstitial lung disease. *Can Resipr J* 2010;17:282-6.

66. Minai OA, Sahoo D, Chapman JT et al. Vaso-active therapy can improve 6-min walk distance in patients with pulmonary hypertension and fibrotic interstitial lung disease. *Respir Med* 2008;102:1015-20.
67. Ghofrani HA, Osterloh IH, Grimminger F et al. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nat Rev Drug Discov* 2006;5:689-702.
68. Ghofrani HA, Wiedemann R, Rose F et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet* 2002;360:895-900.
69. 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;160:600-7.
70. Zisman DA, Schwarz M, Anstrosm KJ et al.; Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med* 2010;363:620-8.
71. Distler JH, Distler O. Imatinib as a novel therapeutic approach for fibrotic disorders. *Rheumatology (Oxford)* 2009;48:2-4.
72. Schermuly RT, Dony E, Ghofrani HA et al. Reversal of experimental pulmonary hypertension by PDGF inhibition. *J Clin Invest* 2005;115:2811-21.
73. Daniels CE, Wilkes MC, Edens M et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. *J Clin Invest* 2004;114:1308-16.
74. Abe K, Toba M, Alzoubi A et al. Tyrosine kinase inhibitors are potent acute pulmonary vasodilators in rats. *Am J Respir Cell Mol Biol* 2011;45:804-8.
75. Ghofrani HA, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2005;353:1412-3.
76. Patterson KC, Weissmann A, Ahmadi T et al. Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. *Ann Intern Med* 2006;145:152-3.
77. Souza R, Sitbon O, Parent F et al. Long term imatinib treatment in pulmonary arterial hypertension. *Thorax* 2006;61:736.
78. Ghofrani HA, Morrell NW, Hoeper MM et al. Imatinib in pulmonary arterial hypertension patients with inadequate response to established therapy. *Am J Respir Crit Care Med* 2010;182:1171-7.
79. Daniels CE, Lasky JA, Limper AH et al.; Imatinib-IPF Study Investigators. Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. *Am J Respir Crit Care Med* 2010;181:604-10.
80. Spiera RF, Gordon JK, Mersten JN et al. Imatinib mesylate (Gleevec) in the treatment of diffuse cutaneous systemic sclerosis: results of a 1-year, Phase IIa, single-arm, open-label clinical trial. *Ann Rheum Dis* 2011;70:1003-9.
81. Khanna D, Sagger R, Mayes MD et al. A one-year, Phase I/IIa, open-label pilot trial of imatinib mesylate in the treatment of systemic sclerosis-associated active interstitial lung disease. *Arthritis Rheum* 2011;63:3540-6.
82. Pope J, McBain D, Petrlich L et al. Imatinib in active diffuse cutaneous systemic sclerosis: results of a six-month, randomized, double-blind, placebo-controlled, proof-of-concept pilot study at a single center. *Arthritis Rheum* 2011;63:3547-51.
83. Orens JB, Estenne M, Arcasoy S et al. International guidelines for the selection of lung transplantation candidates: 2006 update - a consensus report from the Pulmonary Scientific Council in the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006;25:745-55.
84. Schachna L, Medsger TA Jr, Dauber JH et al. Lung transplantation in scleroderma compared with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension. *Arthritis Rheum* 2006;54:3954-61.
85. Sagger R, Khanna D, Furst DE et al. Systemic sclerosis and bilateral lung transplantation: a single centre experience. *Eur Resp J* 2010;36:893-900.

膠原病性肺動脈性肺高血圧症治療の新展開
～早期介入・免疫抑制療法～

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肺動脈性高血圧症(pulmonary arterial hypertension：PAH)は予後不良の難治性病態である．近年，肺血管拡張作用を有する分子標的薬が導入され，短期の自覚症状，血行動態の改善が得られているが，長期予後の改善はいまだ十分でない．強皮症性PAHでは，レイノー現象出現からPAH診断まで10年以上を要することから，定期的なスクリーニングによる早期発見，介入が可能である．また，作用機序の異なる薬剤を初回から併用すべきである．全身性エリテマトーデスに伴うPAHでは，疾患活動性を有して進行のはやい場合はPAH治療薬に強力な免疫抑制療法を組み合わせる．これらの積極的な取り組みにより膠原病性PAHの更なる生命予後の改善が望まれる．

はじめに

肺動脈性肺高血圧症(pulmonary arterial hypertension：PAH)は膠原病に残された難治性病態の1つである．最近，肺動脈平滑筋を標的としたPAHを適応症とする治療薬(以下，PAH治療薬とよぶ)がつぎつぎに承認され，膠原病性PAHの診療に導入された．PAH治療薬の使用により多くの症例で自覚症状や血行動態の改善がみられ，コホート調査では少なくとも短期の生存率延長効果が示されている．ちなみに，われわれのコホートでは，PAH治療薬が導入された前後で3年生存率が26%から78%まで改善している[1]．膠原病性PAHとして一括されることが多いが，基礎疾患や併存病態はきわめて多様である．また，治療の選択肢は3系統のPAH治療薬(プロスタサイクリン誘導体，エンドセリン受容体拮抗薬，ホスホジエステラーゼ(PDE)5阻害薬)に加え，ステロイドや免疫抑制薬など多岐にわたる．したがって，個々の症例の病態，重症度を把握したうえで個別化医療を実践する必要がある．本稿では，膠原病性PAHの更なる予後改善のためにわれわれの実施している取り組みを紹介したい．

〔キーワード〕
強皮症
全身性エリテマトーデス
肺高血圧症
分子標的薬
間質性肺疾患

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1．膠原病性PAHの特徴

PAHはさまざまな膠原病を基礎に発症するが，日本人では混合性結合組織病(mixed connective tissue disease：MCTD)，全身性エリテマトーデス(systemic lupus erythematosus：SLE)，全身性強皮症(systemic sclerosis：SSc)が3大疾患である[1]．基礎疾患によりPAH病態は大きく異なるが，SLEとSScの2つに分類すると理解しやすい(**表1**)[1]．PAHの頻度はSScの方が高く，死因に占め

表 1. SLE-PAH と SSc-PAH の臨床特徴

	SSc-PAH	SLE-PAH
頻度	＜10%	＜2%
死因に占める割合	20～30%	＜10%
生命予後	不良	良好
(PAH 治療薬使用下)	(3 年生存率 50%)	(3 年生存率 90%)
PAH 診断時年齢	60 歳以上	20～30 歳代
PAH 診断までの罹病期間	10 年以上	＜1 年が半数
PAH に影響を与える併存病態	間質性肺疾患 心筋病変 (拡張・収縮障害)	時に収縮性心膜炎 肺血栓塞栓症
免疫抑制療法に対する反応性(短期)	不良	良好

る割合も大きい．SSc-PAH は生命予後が不良で，少なくとも 2 剤以上の PAH 治療薬が使用可能になった 2005 年以降のコホートでも 3 年生存率は 40～60%である[2)3)]．SLE-PAH は 20～30 歳代の若年者が多く，SLE の発症から PAH 診断までの期間が 1 年未満の例が半数を占める．多くは SLE 診断時に呼吸苦の急速な進行を伴い PAH と診断されている．一方，SSc ではレイノー現象の出現から PAH の診断まで 10 年以上を要する例がほとんどで，20 年以上経過している例も少なくない．そのため，PAH 診断時には 60 歳以上の高齢者が大半である．SSc-PAH では間質性肺疾患(interstitial lung disease：ILD)や心筋障害(拡張・収縮能の低下)を併存することが多く，これら併存病態が予後不良要因となる．SLE-PAH では免疫抑制療法により自覚症状や血行動態の改善を経験するが，SSc-PAH では免疫抑制療法は通常無効である．このように SLE-PAH と SSc-PAH は明らかに異なる臨床像を呈することから，膠原病性 PAH として一括することは適切でない．病態的にも，SLE-PAH は肺血管の炎症(血管炎)，SSc-PAH は肺血管壁のリモデリングが中心と推測される．なお，MCTD は SSc，SLE 症状が併存するが，PAH の特徴がどちらに合致するかで層別化が可能である．

2．SSc-PAH の早期診断

SSc では限局皮膚硬化型 SSc (limited cutaneous SSc：lcSSc)が 10 年以上のながい罹病期間の後に PAH と診断される例が大半である．したがって，定期的なスクリーニングをすることで PAH を早期に発見することが可能である．PAH の初期症状は労作時息切れであるが，SSc では ILD，心筋障害，胃食道逆流症，関節拘縮，四肢筋力低下などさまざまな要因が息切れの原因となる．そのため，自覚症状の有無にかかわらず年 1 回の定期的なスクリーニングを実施することが望ましい．スクリーニングとしてひろく用いられている検査はドプラ法を含めた経胸壁心エコーである．肺機能検査，脳性ナトリウム利尿ペプチド(brain natriuretic peptide：BNP)を組み合わせることで，さらに詳細な評価が可能となる．**図 1** にわれわれの施設で実施しているスクリーニングを示す．SSc では ILD，心筋障害を伴うことも多いことから，PAH だけでなく心肺病変の包括的評価が必要である．

ドプラ心エコーにより求めた三尖弁逆流ジェット速度から計算した三尖弁逆流最大圧格差に，推

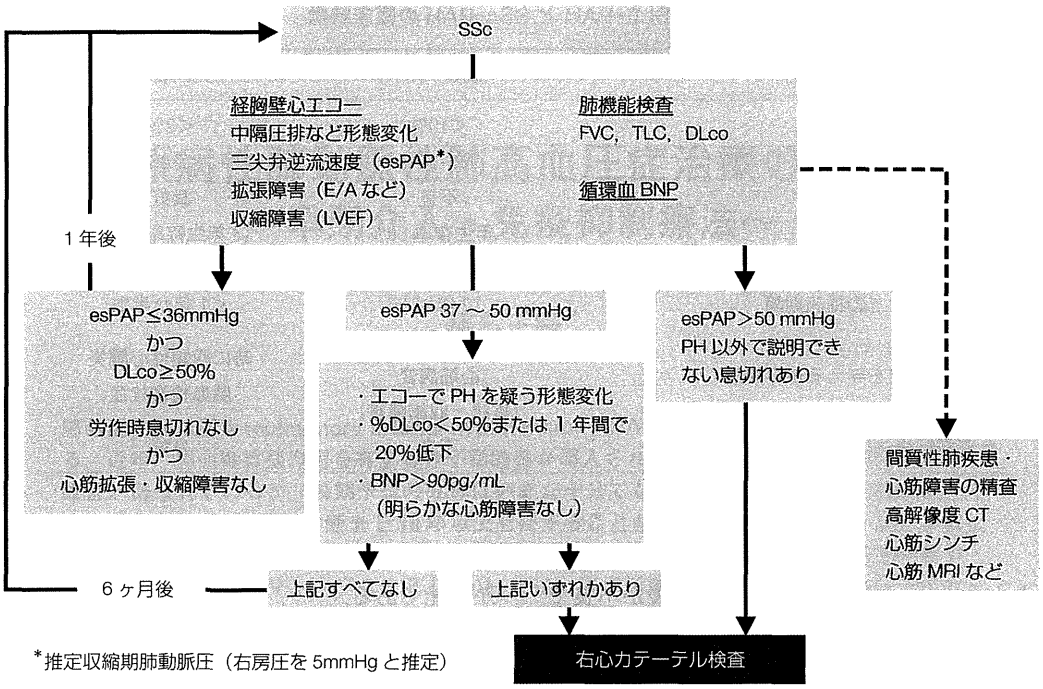

図 1. SSc における PAH スクリーニング

定右房圧（通常は 5 mmHg）を足した推定収縮期肺動脈圧（estimated systolic pulmonary arterial pressure：esPAP）が汎用されている．しかし，esPAP と右心カテーテルで測定した肺動脈圧実測値の相関は必ずしも強くなく，とくに境界域では解離がしばしばみられる[4]．そのため，確定診断には必ず右心カテーテル検査を実施すべきである．SSc では左心疾患や ILD に伴う肺高血圧症をきたす場合があることから[5]，PAH の診断にはそれらの除外が必要である．

3．SSc-PAH の治療

SSc-PAH では複数の PAH 治療薬の使用が可能になっても長期の生命予後の改善効果は明確でなく，PAH 診断 3 年後には半数近くが死亡している[1)~3)]．その原因として SSc-PAH の肺動脈では血管平滑筋増殖より内膜線維化が主体であることや，毛細血管や静脈病変を高率に伴うなど肺血管病変自体の特殊性があげられる[6]．また，併発する ILD や心筋病変が血行動態や肺動脈リモデリングを悪化させる．さらに，高度 ILD が併存する場合，PAH 治療薬の投与が換気血流ミスマッチを悪化させることがある．とくに，最も強力な肺血管拡張作用を有するエポプロステノールの使用が制限されることは PAH 治療の大きな障害となる．

そこで，SSc-PAH 克服のために実施可能な対処法として早期発見・治療介入と，早期からの積極的な PAH 治療薬の併用があげられる．現状の治療アルゴリズムでは治療開始 3～6ヵ月で血行動態を含めた再評価により治療効果を判定し，不十分であれば異なる系統の薬剤を併用する段階的（sequential）併用療法が推奨されている[7]．しかし，SSc-PAH では併用のたびに一時的な効果が得られても，次第に効果が減弱し，最終的には 3 剤を併用しても血行動態悪化を阻止できないケー

スを多く経験してきた．そのため，最近は，PAHと診断した時点から2系統以上のPAH治療薬を同時もしくは1ヵ月以内に開始する早期(up-front)併用療法を実践している．残念ながら現時点で早期介入や早期併用療法が生命予後を改善するエビデンスはないが，今後の構築を期待したい．

4．SLE-PAHの治療

SLE-PAHの一部で免疫抑制療法が著効し，血行動態が正常化することが古くから知られている．これまで対照群を設定した前向き比較試験はないが，免疫抑制療法に反応する症例の特徴として，①基礎疾患としてSLEまたはMCTD[8]，②PAH診断あるいは増悪時に発熱，紅斑，腎炎，抗二本鎖DNA抗体高値，低血清補体価など疾患活動性を伴い，③PAHが進行性，などが知られている．これらの条件を満たす例では大量ステロイドと免疫抑制薬を併用する．有効例では比較的すみやかに自覚症状や血行動態が改善する．SLEの免疫異常を基礎とした肺血管炎が主たる病態と考えられる．そのため，発症早期にタイミングよく免疫抑制療法を導入すると肺動脈圧が正常となりPAHの寛解が得られる．しかし，免疫抑制療法単独でPAHの寛解導入とその長期間の維持を達成することは難しく，われわれの集計でも免疫抑制療法の有無で長期の生命予後に差はない[1]．肺血管炎が遷延すると血管内皮障害や局所のサイトカイン・ケモカイン発現が肺血管リモデリングを促進するため，初回治療時に肺血管炎を沈静化することが大切で，禁忌がないかぎりステロイド大量と間欠的シクロホスファミド静注療法を実施している．免疫抑制療法の効果はリモデリングが進んだ肺血管に対して期待できないことから，早期に肺動脈圧が正常化しない場合はすみやかにPAH治療薬を併用すべきである．

おわりに

PAH治療薬が臨床に導入されたにもかかわらず，膠原病性PAHが難治性病態である状況は解消されていない．更なる予後改善のためには，個々の症例の病態を理解することで治療の最適化に取り組むことが大切である．

文　献

1) Shirai Y *et al*：Clinical characteristics and survival of Japanese patients with connective tissue disease and pulmonary arterial hypertension：a single-center cohort. *Rheumatology* (in press)
2) Condliffe R *et al*：Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* **179**：151-157, 2009
3) Mathai SC *et al*：Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases：impact of interstitial lung disease. *Arthritis Rheum* **60**：569-577, 2009
4) Mukerjee D *et al*：Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. *Rheumatology* **43**：461-466, 2004
5) Avouac J *et al*：Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *J Rheumatol* **37**：2290-2298, 2010
6) Overbeek MJ *et al*：Pulmonary arterial hypertension in limited cutaneous systemic sclerosis：a distinctive vasculopathy. *Eur Respir J* **34**：371-379, 2009
7) Barst RJ *et al*：Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* **54**：S78-84, 2009
8) Sanchez O *et al*：Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest* **130**：182-189, 2006

膠原病疾患に伴う肺高血圧：強皮症に合併する肺高血圧を中心に

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KEY WORDS
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Pulmonary hypertension associated with systemic sclerosis.
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はじめに

近年，新規治療法の導入や対症・支持療法の進歩により，膠原病患者の生命予後は著しく改善した。一方で，依然として治療に対する反応性が不良の難治性病態が残されており，その代表が肺高血圧症（pulmonary hypertension；PH）である。近年，血管平滑筋を主な治療標的とした分子標的療法が導入され，PH診療は新たな時代を迎えている。しかしながら，膠原病患者の死因に占めるPHの割合は年々増えており，いまだ満足できる治療成果は得られていない。本稿では，膠原病に伴うPHについて，特に予後不良の全身性強皮症（systemic sclerosis；SSc）に焦点を絞り，最近の知見を総括する。

Ⅰ．疫　学

PHはさまざまな膠原病を基礎に発症するが，頻度の高い疾患としてSScが知られている。欧米の報告ではSScにおけるPHの頻度は７～12%で，膠原病に伴うPHの70%以上を占める[1]。フランスで実施された前向き調査では，SScにおけるPH新規発症率は1.37/患者・年とされる[2]。一方，わが国ではPHの基礎疾患として全身性エリテマトーデス（systemic lupus erythematosus；SLE）や混合性結合組織病（mixed connective tissue disease；MCTD）も多くみられ，膠原病に伴うPHに占めるSScの割合は１/３程度に過ぎない[3]。

SScでは肺動脈性肺高血圧症（pulmonary arterial hypertension；PAH）だけでなく左心疾患や間質性肺疾患（interstitial lung disease；ILD）に伴うPHなど多彩なPH病態がみられ，欧州のコホートではSSc関連PHに占めるPAHの割合が51%，ILDに伴うPHが27%，左心疾患に伴うPHが20%，肺

表．PAH治療薬使用下でのSSc関連PAHの生命予後

発表者	報告国	症例数	基礎疾患	PAH診断からの累積生存率		
				1年	2年	3年
Mathai (2009)[6]	米国	39	SSc (ILDなし)	87%	79%	64%
Mathai (2009)[6]	米国	20	SSc (ILDあり)	82%	46%	39%
Hachulla (2009)[7]	フランス	47	SSc	75%	68%	56%
Condliffe (2009)[8]	英国	259	SSc	78%	58%	47%
Hesselstrand (2011)[9]	スウェーデン	30	SSc	86%	59%	39%

静脈性閉塞性疾患 (pulmonary veno-occlusive disease；PVOD) が２％と報告されている[1]。PAHは限局皮膚硬化型と呼ばれる軽症例に多く，レイノー現象出現から10年以上の高齢者 (60歳以上) がほとんどである。この点は20～30歳代の若年者に多いMCTD，SLEと大きく異なる[3]。SSc関連PAHでは抗セントロメア抗体が高率に検出されるが，左心疾患やILDに伴うPHはびまん皮膚硬化型に多い。

Ⅱ．生命予後と病態

PAH治療薬登場前には，SSc関連PHの１年生存率はわずか50%，３年生存率は20%以下ときわめて予後不良であった[4]。PAHに対象を絞って特発性PAHと生存率を比較した調査でも，SScのほうが予後不良である[5]。一方，少なくとも２剤以上のPAH治療薬が使用可能になった以降にPAHと診断された症例コホートの治療成績を表に示す[6)-9)]。多くのコホートで診断後１年までは80%以上の生存率を維持し，明らかに改善している。ただし，３年生存率は半数以上のコホートで50%に満たない。単剤による初回治療が中心で，診断時にWHO機能分類Ⅲ度が大半である点を勘案しても，SSc関連PAHは今なお予後不良の病態である。

一方，膠原病関連PAHの生命予後は基礎疾患により異なることが知られており，欧米の複数の報告でSScはSLE，MCTDに比べて予後不良である[8)10)]。その理由として以下の要因があげられる。

１．肺血管病変の特殊性

SScでみられる末梢血管病変に共通する所見は細胞成分に乏しい内膜の線維化で，中心性に血管内腔を狭窄し，ときに完全に閉塞する。PAHでは特発性PAHや他の膠原病に伴うPAHと異なり，血管平滑筋の増殖病変は少ない[11]。また，内膜線維化は比較的サイズの太い筋性動脈から毛細血管，細静脈まで広範囲に及び，PVODを高率に併発する。興味深いことに，PAHに特徴的とされる叢状病変はきわめてまれである。このように，SSc関連PAHは組織学的にきわめてユニークで，現状のPAH治療薬が主たる標的とする血管平滑筋の増殖病変に乏しいことが治療反応性不良の要因の１つである。

２．心筋障害の併存

SScでは心筋の持続的な循環障害による微細な心筋線維化を高率に伴う。剖検では80%以上に観察されるが，うっ血性心不全や治療を要する不整脈を呈する例は10%程度に過ぎない。ただし，PAHなど心筋に負荷がかかる状況では血行動態を悪化させる要因になる。そのため，SSc関連PAHでは肺動脈圧に比して心拍出量が相対的に低い[8)10)]。また，SSc関連PAHで肺毛細血管楔入圧が15mmHg前後の境界値の症例が多いことも，左心系の拡張障害が潜在的に存在することを示唆する。

３．ILDの併存

SSc関連PAHの約半数に軽度のILDが併存し，併発例では非併発例に比べて生命予後が悪い[6)12)]。肺胞構造の破壊により肺内シャントが潜在的に存在すると，PAH治療薬投与により換気の悪い領域の血流が増えることで肺内シャントが増加し，酸素化を悪化させる場合がある[13]。そのため，PAH治療薬の使用により低酸素血症が増悪することをしばしば経験する。特に高用量のエポプロステノールでは必発である。

Ⅲ．PHスクリーニングの重要性

PHの初期症状は軽度かつ非特異的で，通常は労作時の息切れである。SScではILD，心筋障害，胃食道逆流症，関節拘縮，四肢筋力低下などが息切れの要因になることから，自覚症状から早期のPHを発見することはきわめて困難である。そのため，PH高リスク集団であるSScでは，自覚症状の有無にかかわらず定期的なスクリーニ