Pulmonary hypertension phenotypes in patients with systemic sclerosis

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Different forms of pulmonary hypertension can be present in patients with systemic sclerosis. In this article we review the epidemiology, diagnosis, outcomes and treatment of the spectrum of pulmonary vascular phenotypes associated with systemic sclerosis. https://bit.ly/3xUwrVB

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Abstract

Pulmonary hypertension (PH) commonly affects patients with systemic sclerosis (SSc) and is associated with significant morbidity and increased mortality. PH is a heterogenous condition and several different forms can be associated with SSc, including pulmonary arterial hypertension (PAH) resulting from a pulmonary arterial vasculopathy, PH due to left heart disease and PH due to interstitial lung disease. The incidence of pulmonary veno-occlusive disease is also increased. Accurate and early diagnosis to allow optimal treatment is, therefore, essential. Recent changes to diagnostic haemodynamic criteria at the 6th World Symposium on Pulmonary Hypertension have resulted in therapeutic uncertainty regarding patients with borderline pulmonary haemodynamics. Furthermore, the optimal pulmonary vascular resistance threshold for diagnosing PAH and the role of exercise in identifying early disease require further elucidation. In this article we review the epidemiology, diagnosis, outcomes and treatment of the spectrum of pulmonary vascular phenotypes associated with SSc.

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disorder characterised by inflammation, excessive collagen deposition and fibrosis [1]. Limited cutaneous systemic sclerosis (LcSSc) is characterised by skin thickening distal to the elbows and knees, with or without facial and neck involvement, and the frequent presence of anti-centromere antibodies, while diffuse cutaneous systemic sclerosis (DcSSc) is characterised by proximal skin thickening and a predominance of anti-topoisomerase 1 (Scl-70) antibodies and anti-RNA polymerase III antibodies [2]. Earlier and more frequent organ involvement occurs in DcSSc [3]. A small proportion of patients may present with clinical features of SSc in the absence of skin thickening (SSc sine scleroderma).

Pulmonary hypertension (PH) describes a heterogenous group of conditions defined by an elevated mean pulmonary arterial pressure (mPAP). Five classification groups are described: Group 1: pulmonary arterial hypertension (PAH); Group 2: PH due to left heart disease (PH-LHD); Group 3: PH due to lung diseases and/or hypoxia (PH-lung); Group 4: PH due to pulmonary artery obstructions; Group 5: PH with unclear and/or multifactorial mechanisms (figure 1) [5]. PAH is characterised by a progressive pulmonary arterial vasculopathy. Subsequent increased pulmonary vascular resistance (PVR) and pulmonary arterial pressure lead to increased right ventricular (RV) afterload with subsequent RV dysfunction, failure and premature death [6–8]. Despite the availability of specific therapies targeting three main pathways, PAH associated with SSc (SSc-PAH) is associated with a poor prognosis with 3-year survival of only 52% [9]. Patients with SSc may also develop other forms of PH (SSc-PH), especially PH-LHD (SSc-PH-LHD) and PH-lung

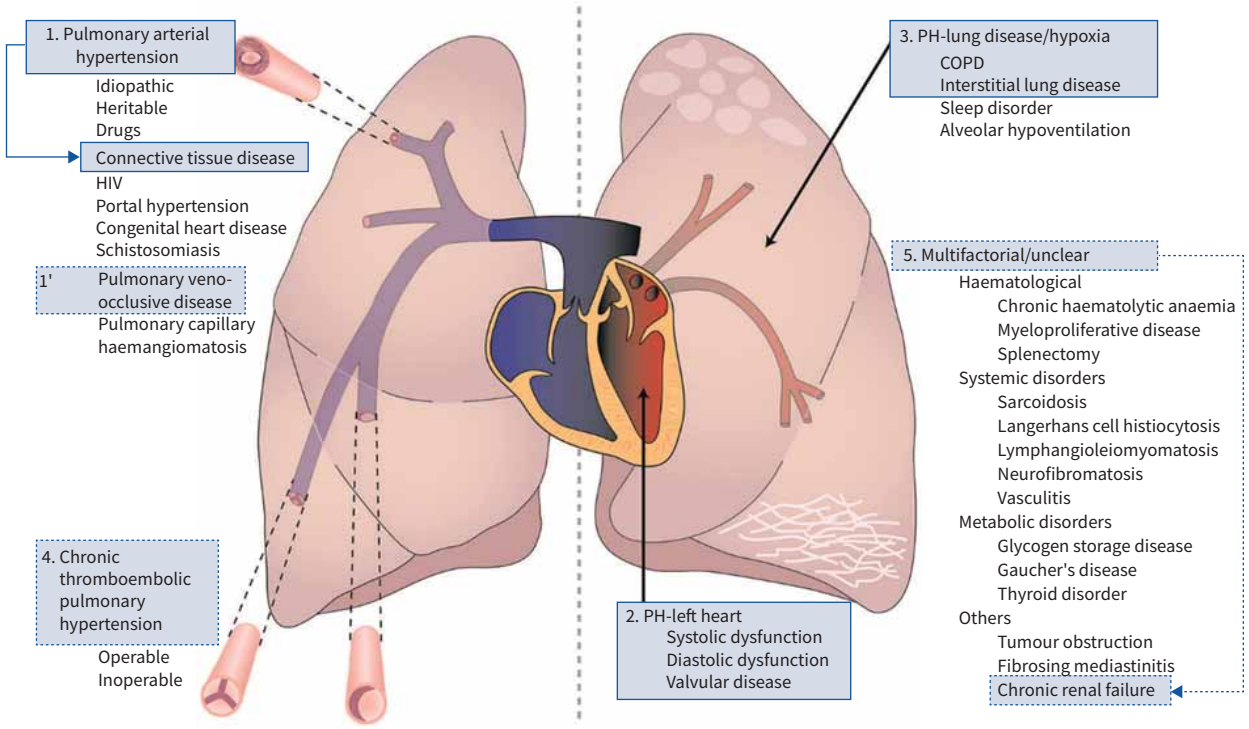

FIGURE 1 Potential pulmonary hypertension (PH) classification groups associated with systemic sclerosis. Patients may develop a pulmonary arterial vasculopathy (group 1, pulmonary arterial hypertension), may develop PH due to left heart disease (group 2) or PH due to lung disease (group 3; most commonly interstitial lung disease, although the incidence of combined fibrosis and emphysema is also increased). The incidence of pulmonary veno-occlusive disease (group 1′) also appears to be increased in systemic sclerosis. Chronic thromboembolic PH (group 4) should be excluded while patients with a previous scleroderma renal crisis who progress to end-stage chronic kidney disease may develop group 5 disease. Reproduced and modified from [4] with permission from the publisher.

(SSc-PH-lung). Pulmonary venous involvement may be relatively common in patients diagnosed with SSc-PAH while some patients may present with a predominant picture of pulmonary veno-occlusive disease (PVOD) [10–12]. Patients may also rarely present with group 4 disease, chronic thromboembolic pulmonary hypertension, as SSc is associated with an increased risk of venous thromboembolism [13].

Diagnostic criteria with regard to the threshold of mPAP used to define the presence of PH, the use or non-use of a threshold for PVR to diagnose PAH, and the presence or absence of the entity of PH on exercise (PH-exercise) have changed over recent years (table 1). Furthermore, there are now a group of patients with elevated mPAP but normal PVR who are unclassifiable according to the most recent World Symposium on Pulmonary Hypertension (WSPH). Making the correct diagnosis regarding the form of SSc-PH is of critical importance in informing prognosis and guiding the most appropriate management strategy. Therefore, in this article we review the different PH phenotypes present in patients with SSc (table 2).

Methods

A PubMed systematic literature search was undertaken using the following search criteria:

((Systemic sclerosis) OR (Scleroderma) OR (Limited cutaneous systemic sclerosis) OR (Diffuse cutaneous systemic sclerosis)) AND ((Pulmonary hypertension) OR (Pulmonary arterial hypertension)) AND ((Exercise) OR (Borderline) OR (Interstitial lung disease) OR (ILD) OR (Diffusion capacity) OR (Left heart disease) OR (DLCO) OR (Transfer factor) OR (Phenotype)).

218 search results were all analysed for relevant information. Furthermore, a grey search of the manuscripts cited within these articles was undertaken together with the inclusion of key legacy papers.

Changing definitions of PH

The first WSPH was organised by the World Health Organization (WHO) in 1973 in response to a European epidemic of appetite suppressant-induced PH [14]. It defined PH by a mPAP at right heart

TABLE 1 Haemodynamic diagnostic criteria of the six World Symposia on Pulmonary Hypertension (WSPH)

	First WSPH [14]	Second WSPH [15]	Third WSPH [16]	Fourth WSPH [17, 18]	Fifth WSPH [19, 20]	Sixth WSPH [5, 21]
Year	1973	1998	2003	2008	2013	2018
Location	Geneva, Switzerland	Evian, France	Venice, Italy	Dana Point, CA, USA	Nice, France	Nice, France
mPAP PH diagnostic threshold	>25 mmHg	Not defined	>25 mmHg	⩾25 mmHg	⩾25 mmHg	>20 mmHg
PVR included in PAH definition	No	No	>3 WU	No	>3 WU	⩾3 WU
PAWP post-capillary threshold	Discussed but not defined	Not discussed	>15 mmHg	⩾15 mmHg	>15 mmHg	>15 mmHg
Isolated post-capillary PH	Not discussed	Not discussed	Not discussed	PVR <3 WU[#] TPG ⩽12 mmHg	DPG <7 mmHg	PVR <3 WU
Combined pre- and post-capillary PH	Not discussed	Not discussed	Not discussed	PVR ⩾3 WU[¶] TPG >12 mmHg	DPG ⩾7 mmHg	PVR >3 WU
PH-exercise	Discussed but not defined	Not discussed	>30 mmHg	No	No	No
mPAP 21–24 mmHg	20 mmHg as upper limit of normal recognised	Not discussed	Not discussed	Uncertainty in patients with mPAP 21–24 mmHg	At-risk patients (*e.g.* CTD) should be followed closely	Most now defined as PH; however, mPAP >20 mmHg, PAWP ⩽15 mmHg but PVR <3 WU not classified

mPAP: mean pulmonary arterial pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension; PAWP: pulmonary arterial wedge pressure; WU: Wood Units; TPG: transpulmonary gradient; DPG: diastolic pulmonary gradient; CTD: connective tissue disease. [#]: termed "diastolic heart failure"; [¶]: termed "pre-capillary PH and diastolic dysfunction".

catheterisation (RHC) >25 mmHg (table 1) [14]. This haemodynamic definition was derived from the recommendation of a previous WHO report on cor pulmonale, published in 1961 [22]. The diagnostic threshold of 25 mmHg would remain until the sixth WSPH in 2018 where it was proposed that the threshold be reduced to >20 mmHg [5]. This change in definition was suggested following a systematic

TABLE 2 Systemic sclerosis (SSc)-pulmonary hypertension (PH) phenotypes

SSc-PAH: post-6th WSPH	mPAP ⩾20 mmHg, PAWP ⩽15 mmHg, PVR ⩾3 WU
SSc-PAH: pre-6th WSPH	mPAP ⩾25 mmHg, PAWP ⩽15 mmHg, PVR >3 WU
SSc: mPAP >20 mmHg, PVR <3 WU	A group of patients with elevated mPAP who do not fulfil current PH diagnostic criteria of pre- or post-capillary PH
SSc-BoPH	Term used in the literature to describe patients with borderline haemodynamics (mPAP 21–24 mmHg) prior to the current 6th WSPH PH definition
SSc-PH-exercise	Previously, resting mPAP <25 mmHg but mPAP >30 mmHg on exercise; more recent definition (not included in 6th WSPH) suggested as resting mPAP <25 mmHg but mPAP >30 mmHg and TPR >3 WU on exercise
SSc-PVOD	Meets haemodynamic criteria for PAH but radiological and clinical features of PVOD
SSc-PH-LHD	mPAP ⩾20 mmHg, PAWP >15 mmHg
SSc-IpcPH	mPAP ⩾20 mmHg, PAWP >15 mmHg, PVR <3 WU
SSc-CpcPH	mPAP ⩾20 mmHg, PAWP >15 mmHg, PVR ⩾3 WU
SSc-PH-HFpEF	SSc-PH-LHD due to heart failure with preserved ejection fraction
SSc-PH-HFrEF	SSc-PH-LHD due to heart failure with reduced ejection fraction
SSc-PH-ILD	mPAP ⩾20 mmHg, PAWP ⩽15 mmHg, PVR ⩾3 WU in the presence of significant ILD (often defined as HRCT showing >20% fibrotic lung involvement and/or FVC <70% predicted)

PAH: pulmonary arterial hypertension; WSPH: World Symposium on Pulmonary Hypertension; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; WU: Wood Units; BoPH: borderline PH; PVOD: pulmonary veno-occlusive disease; LHD: left heart disease; IpcPH: isolated post-capillary PH; CpcPH: combined pre- and post-capillary PH; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; ILD: interstitial lung disease; PAWP: pulmonary arterial wedge pressure; TPR: total pulmonary resistance; HRCT: high-resolution computed tomography; FVC: forced vital capacity.

review by Kovacs *et al.* [23] which demonstrated that the mean mPAP within the healthy population was 14.0±3.3 mmHg. In addition, Maron *et al.* [24] reviewed RHC data from 21 727 patients in the US Veterans healthcare system and observed increased mortality in patients with a mPAP 19–24 mmHg compared with <19 mmHg. Furthermore, a meta-analysis of 16 482 patients performed by Kolte *et al.* [25] also identified increased mortality in patients with mPAP >19 mmHg. It is interesting to note that although the 1961 report proposed a threshold of 25 mmHg, it also commented that the upper limit of normal for mPAP was 15 mmHg [22]. Furthermore, the first WSPH also stated that the mPAP at rest "never" exceeded 20 mmHg in healthy individuals [14]. The uncertain nature of patients with mPAP 21–24 mmHg had been recognised at the fourth and fifth World Symposia, but there were deemed to be insufficient data to introduce a formal definition of "borderline PH" [18, 19].

The effects of exercise on mPAP were discussed at the first WSPH, but were not included in diagnostic criteria [13]. By the third WSPH, a diagnostic threshold of mPAP >30 mmHg for the diagnosis of PH-exercise had been introduced [17, 26]. PH-exercise was, however, dropped from the diagnostic criteria in the fourth WSPH in 2008 as it was appreciated that mPAP may frequently increase >30 mmHg on exercise in normal individuals, especially those aged >50 years [17].

PVR was incorporated into the definition of PAH at the third WSPH using a threshold of >3 Wood Units (WU) [27]. Its inclusion in the definition aimed to prevent patients with flow-related increases in mPAP being diagnosed with PAH. Although it was temporarily absent from the fourth WSPH, it was reinserted into the diagnostic criteria for PAH at the fifth WSPH, albeit with the slight change of including patients with a PVR ⩾3 WU (as opposed to >3 WU) [19].

Left atrial pressure, most commonly assessed by the pulmonary arterial wedge pressure (PAWP), was introduced in the third WSPH to differentiate between pre-capillary (PAWP ⩽15 mmHg) and post-capillary PH (PAWP >15 mmHg) [16].

Summary

Haemodynamic criteria for different forms of PH have changed over recent decades. The most recent WSPH defines pre-capillary PH as mPAP >20 mmHg, PAWP ⩽15 mmHg and PVR ⩾3 WU.

SSc-PAH

Estimates of the prevalence of PAH within the SSc population range between 6.4% and 9% [27, 28]. The incidence of SSc-PAH in patients with LcSSc and DcSSc is 1.25 and 0.4 cases per 100 patient-years, respectively [29]. Meta-analysis involving 3818 patients with RHC-confirmed PH identified PAH as the most common form of PH seen in SSc, comprising 63% of RHC-confirmed cases [27]. There may, however, be ascertainment bias in these data due to patients with other forms of PH being less likely to undergo RHC. Historically, SSc-PAH was associated with a poor prognosis with a 3-year survival of 30% [30]. Mortality remains high despite the availability of PAH-specific therapy. Lefèvre *et al.* [9] observed 1- and 3-year survival rates of 81% and 52%, respectively, in a meta-analysis.

Several studies have demonstrated that, despite having less severe pulmonary haemodynamics, survival of patients with SSc-PAH is worse than with idiopathic PAH (IPAH) [31–37]. There are several possible explanations for this including differences in patient characteristics, the underlying pulmonary arterial vasculopathy, and the ability of the RV to compensate for increased afterload.

Patient characteristics

When compared with IPAH, patients with SSc-PAH are older with a lower coefficient for diffusing capacity of the lung for carbon monoxide (D_{LCO}). In a multivariate analysis of 375 IPAH and SSc-PAH patients, Ramjug *et al.* [37] identified that higher age and lower D_{LCO} were independent prognostic markers. The lower D_{LCO} may reflect increased alveolar-capillary block due to overt or covert interstitial lung disease (ILD), reduced capillary blood volume related to the nature of the pulmonary vasculopathy or a component of PVOD. The multisystem nature of SSc, with involvement not only of the lungs and heart, but also the skin, gastrointestinal tract and kidneys, likely also impacts survival [38, 39].

Vasculopathy

Overbeek *et al.* [12] demonstrated intimal fibrosis in histological specimens from all eight patients they studied with SSc-PAH compared with only three out of 11 patients with IPAH. Plexiform lesions were much less common than in patients with IPAH. Similarly, Dorfmüller *et al.* [11] observed marked muscular artery intimal fibrosis in four out of four SSc-PAH patients in contrast with only four out of 29

patients with IPAH. In addition to differences in pulmonary arterial histology, there may also be an increased frequency of pulmonary venous lesions in SSc-PAH (see PVOD section) [40].

Right ventricle

Overbeek *et al.* [41] demonstrated poorer RV contractility in 13 patients with SSc-PAH compared with 17 IPAH patients. Similarly, Tedford *et al.* [42] observed worse RV contractility and coupling of RV contractility with afterload in seven SSc-PAH patients compared with five IPAH patients. Mathai *et al.* [43] found N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in 55 SSc-PAH patients to be significantly higher than in 43 IPAH patients, despite the IPAH group having more severe PH. Furthermore, although Overbeek *et al.* [41] found no difference in the extent of interstitial fibrosis in the RVs obtained at autopsy of five SSc-PAH and nine IPAH patients, there was an increased inflammatory myocardial infiltrate in the SSc-PAH group. Conversely, Hsu *et al.* [44] observed increased interstitial fibrosis in RV endomyocardial biopsies obtained from 11 SSc-PAH patients when compared with seven IPAH patients and six SSc patients without PH. Interestingly, when compared with healthy controls, sarcomere function (as assessed by the maximum calcium-activated force) was significantly lower in SSc-PAH but significantly higher in IPAH. Sarcomere function in SSc patients without PH was intermediate between the controls and SSc-PAH.

Medical therapy in SSc-PAH

Current therapies for PAH target three main pathways: nitric oxide, endothelin-1 and prostacyclin [45, 46]. A number of randomised controlled trials (RCTs) have published data on outcomes in patients with connective tissue disease (CTD), the majority of whom had SSc (table 3) [63]. With the exception of an unblinded RCT of epoprostenol, short-term monotherapy RCTs have tended to report lower response to therapy in patients with CTD associated PAH (CTD-PAH) [64, 65]. However, newer data from longer studies where the majority of patients have received combination therapy have challenged these findings [54, 56, 61].

Screening

Humbert *et al.* [66] observed milder haemodynamics and superior survival in a cohort of SSc patients identified in a screening programme as compared to presenting symptomatically. Although lead-time bias cannot be excluded as a cause of the superior survival, subsequent RCTs of PAH therapies have demonstrated larger treatment response of patients in functional class (FC) II compared with FC III [67]. There is, therefore, a good rationale for screening asymptomatic SSc patients to enable earlier treatment [68]. Coghlan *et al.* [69] compared the multi-modality 2-step DETECT algorithm with the European Respiratory Society/European Society of Cardiology (ERS/ESC) approach of echocardiography alone and observed sensitivity/specificity for identifying PAH (mPAP $\geqslant$25 mmHg and PAWP $\leqslant$15 mmHg) of 96%/48% and 71%/69%, respectively. The Australian Scleroderma Interest Group (ASIG) studied an approach using pulmonary function tests and NT-proBNP and reported sensitivity/specificity for identifying PAH of 94%/55% compared with 95%/32% for the ERS/ESC approach [70]. Hao *et al.* [71] compared all three approaches in 73 patients and observed that although the DETECT and ASIG approaches performed similarly, the ASIG algorithm reduced the need for RHC without missing any cases of PAH. A direct comparison of approaches is, however, difficult due to inclusion criteria used in different studies [72].

Although no difference in the incidence of PAH was identified when comparing the DETECT algorithm with an earlier approach involving symptoms, D_{LCO}, NT-proBNP and echocardiography, Hoffmann-Vold *et al.* [73] observed that DETECT identified a significantly higher number of patients with mPAP 21–24 mmHg (31% *versus* 17%).

Summary

Survival in SSc-PAH is worse than in IPAH which may be related to a number of factors including the multisystem nature of SSc and the capacity of the RV to accommodate increased afterload. Data from RCTs of combination therapies with combined morbidity/mortality end-points have, however, reported equivalent outcomes to those seen in IPAH. Patients with SSc-PAH should therefore receive timely dual and triple combination therapy. Asymptomatic SSc patients should be entered into screening programmes.

Impact of the sixth WSPH definition

Two studies investigating the effect of lowering the mPAP diagnostic threshold from $\geqslant$25 to >20 mmHg in patients with SSc have been published. Jaafar *et al.* [74] performed a retrospective, single centre analysis of 268 SSc patients who had undergone RHC [75]. Seven (5%) out of 131 SSc patients without PH according to the old definition were re-classified to either pre-capillary PH (PAH: n=1; PH-lung: n=3) or post-capillary PH (n=3) [74]. In those with mPAP 21–24 mmHg but without significant lung or left heart

TABLE 3 Key randomised controlled trials and sub-group analyses in systemic sclerosis (SSc)-pulmonary arterial hypertension (PAH)

Study [ref.]	Drug	Study length	CTD patients n	CTD type	Outcome in overall/comparator study	Outcomes in CTD sub-group
Nitric oxide pathway						
SUPER-1 [47, 48]	Sildenafil 20 mg, 40 mg, 80 mg three times daily	12 weeks	84	45% SSc, 23% SLE, 32% other	Primary: mean placebo-adjusted change in 6MWD +45 m* (20 mg), +46 m* (40 mg), +50 m* (80 mg) Secondary: improvement in WHO FC in 7% (placebo), 28%* (20 mg), 36%* (40 mg), 42%* (80 mg) mPAP: −2.1 mmHg* (20 mg), −2.6 mmHg* (40 mg), −4.7 mmHg* (80 mg)	Primary: 6MWD −13 m (placebo), +42 m* (20 mg), +36 m NS (40 mg), +15 m NS (80 mg) Secondary: improvement in WHO FC in 5% (placebo), 29%* (20 mg), 40%* (40 mg), 42%* (80 mg) mPAP: −4.6 mmHg* (20 mg), −2.8 mmHg NS (40 mg), −3.2 mmHg NS (80 mg)
PHIRST-1 [49, 50]	Tadalafil 2.5mg–40 mg once daily 53% background Bosentan	16 weeks	56	Unknown	Primary: mean placebo-adjusted change in 6MWD +27 m* (20 mg), +33 m* (40 mg) Secondary: no overall significant effect on WHO FC Time to clinical worsening improved in 40 mg dose*	Primary: exact distances not specified but comparable to IPAH Secondary: higher proportion worsened and lower proportion improved WHO FC in CTD-PAH cf IPAH Higher rate of clinical worsening in 40 mg dose (11% *versus* 4% IPAH)
PATENT-1 [51, 52]	Riociguat up to 2.5 mg three times daily 44% background ERA 6% background prostanoid	12 weeks	111	59% SSc, 16% SLE, 25% other	Primary: treatment arm 6MWD +30 m *versus* placebo −6 m (mean placebo-adjusted change +36 m*) Secondary: placebo: improvement in WHO FC in 14% and worsening in 14%; treatment: improvement in WHO FC in 21% and worsening in 4%* PVR: −9 dyn·s·cm^{-5} (placebo) *versus* −223 dyn·s·cm^{-5} (treatment)* NT-proBNP: +232 pg·mL^{-1} (placebo) *versus* −198 pg·mL^{-1} (treatment)*	Primary: SSc treatment arm 6MWD +4 m *versus* placebo −37 m* Secondary: SSc placebo: improvement in WHO FC in 13% and worsening in 27%; treatment: improvement in WHO FC in 16% and worsening in 2%* PVR: −79 dyn·s·cm^{-5} (placebo) *versus* −132 dyn·s·cm^{-5} (treatment) NT-proBNP: +142 pg·mL^{-1} (placebo) *versus* +98 pg·mL^{-1} (treatment)*
ERA-1						
BREATHE-1 [53]	Bosentan 125–250 mg twice daily	16 weeks	63	75% SSc, 25% SLE	IPAH treatment arm 6MWD +46 m *versus* placebo −5 m*	SSc treatment arm 6MWD +3 m *versus* placebo −40 m
AMBITION [54, 55]	Ambrisentan 10 mg and/or Tadalafil 40 mg once daily	Mean 74 weeks	187	63% SSc, 12% MCTD, 9% SLE	50% risk reduction of combined morbidity/mortality end-point*	56% risk reduction of combined morbidity/mortality end-point*
SERAPHIN [56]	Macitentan 10 mg once daily 64% on background PAH therapy	Mean 115 weeks	224	63% SSc, 12% MCTD, 9% SLE	50% risk reduction of combined morbidity/mortality end-point*	56% risk reduction of combined morbidity/mortality end-point*
Prostanoid						
[57, 58]	Intravenous epoprostenol	12 weeks	111	100% SSc	IPAH study treatment arm +47 m *versus* conventional therapy −66 m* Secondary: mPAP mean placebo-adjusted difference −6.7 mmHg* PVR mean placebo-adjusted difference −4.9 WU*	Primary: treatment arm 6MWD +46 m *versus* conventional therapy −48 m* Secondary: mPAP mean placebo-adjusted difference −6 mmHg* PVR mean placebo-adjusted difference −5.5 WU*
[59, 60]	Subcutaneous treprostinil Background therapy unclear	12 weeks	90	50% SSc, 28% SLE, 19% MCTD	Primary: treatment arm 6MWD median +10 m *versus* placebo +0 m* Secondary: mPAP −2.3 mmHg*, PVRi −3.5 WU·m^{-2}*	Primary: treatment arm 6MWD +24 m *versus* placebo +3 m Secondary: mPAP −3 mmHg, PVRi −4 WU·m^{-2}*

Continued

TABLE 3 Continued

Study [ref.]	Drug	Study length	CTD patients n	CTD type	Outcome in overall/comparator study	Outcomes in CTD sub-group
GRIPHON [61, 62]	Selexipag 200–1600 µg twice daily 80% on background PAH therapy	Mean 70 weeks	334	51% SSc, 25% SLE, 25% MCTD/ other	40% risk reduction of combined morbidity/mortality end-point*	41% risk reduction of combined morbidity/mortality end-point*

CTD: connective tissue disease; ERA-1: endothelin receptor antagonist-1; SLE: systemic lupus erythematosus; 6MWD: 6-min walk distance; WHO FC: World Health Organization functional class; mPAP: mean pulmonary arterial pressure; NS: nonsignificant; IPAH: idiopathic pulmonary arterial hypertension; PVR: pulmonary vascular resistance; NT-proBNP: N-terminal pro-brain natriuretic peptide; MCTD: mixed connective tissue disease; PVRi: PVR index; WU: Wood Units. *: p<0.05.

disease (n=28), a single patient (4% of the 21–24 mmHg group, 1% of the original no PH group) was reclassified as having PAH [74]. The authors also reanalysed 244 patients from the original DETECT cohort [69] and found that four (11%) out of 36 patients with mPAP 21–24 mmHg were reclassified as having PAH. Xanthouli *et al.* [76] subsequently studied 284 SSc patients, 146 (49%) of whom had a mPAP ⩽20 mmHg and 55 (19%) had a mPAP of 21–24 mmHg. Only four patients (7% of the 21–24 mmHg group, 2% of the original no PH group) were reclassified with PAH [76]. The authors of both studies concluded that the new diagnostic criteria (with a change only to the mPAP threshold) had limited impact on the diagnosis of SSc-PAH.

Summary

Changes to the haemodynamic diagnosis of pre-capillary PH proposed at the sixth WSPH have only a modest effect on the number of patients diagnosed with SSc-PAH.

Elevated mPAP with PVR <3 WU

A proportion of SSc patients with normal PAWP who have preserved/mildly impaired cardiac outputs may have a mPAP >20 mmHg but a PVR <3 WU. For example, a SSc patient with a mPAP of 26 mmHg, PAWP 12 mmHg and a cardiac output of 5 $L \cdot min^{-1}$ has a PVR of (26–12)/5=2.8 WU and hence cannot be assigned a PH category. This occurrence will be made more common by the change in diagnostic threshold for mPAP from ⩾25 mmHg to >20 mmHg. In the study by Jaafar *et al.* [74] discussed above, the use of a PVR threshold of 2 WU instead of 3 WU would have resulted in an increase from one to nine PAH re-diagnoses (32% of all patients with mPAP 21–24 mmHg). Similarly, in the study of Xanthouli *et al.* [76], the number of re-diagnoses would have increased from four to 28 (51% of patients with mPAP 21–24 mmHg). The use of a lower PVR threshold for the diagnosis of PAH is supported by several studies.

Xanthouli *et al.* [76] observed that the 28 patients with mPAP 21–24 mmHg but PVR ⩾2 WU had lower 6-min walk distance (6MWD) and TAPSE (tricuspid annulus systolic excursion) and worse survival than patients with a PVR <2 WU. Kovacs *et al.* [77] found the mean PVR in 222 healthy volunteers in the literature to range from 0.77±0.3 WU in people aged <24 years to 1.13±0.5 WU in people aged ⩾70 years. Maron *et al.* [78] retrieved RHC data from 40 082 patients in the US Veterans healthcare system (many with heart failure and/or COPD). In those patients with a mPAP ⩾19 mmHg and PAWP ⩽15 mmHg, the PVR threshold above which the hazard ratio for mortality increased was 2.2 WU. Ratwatte *et al.* [79] recently presented data on 82 patients (42 with CTD) with mPAP ⩾25 mmHg, PAWP ⩽15 mmHg but PVR <3 WU (median (interquartile range) 2.2 (1.9–2.7) WU) who were all treated with PAH-specific therapy. They found that this haemodynamic picture was associated with impaired function and reduced survival but was also associated with functional response to PAH-specific therapy [79].

SSc with mPAP 21–24 mmHg

Although the term "borderline pulmonary hypertension" was never adopted by international guidelines, several studies involving patients with mPAP 21–24 mmHg which were performed prior to changes in diagnostic thresholds in the sixth WSPH used this phrase (table 4). The majority of patients had a PVR <3 WU. These studies suggested that SSc with mPAP 21–24 mmHg is not a benign condition, being associated with a risk of haemodynamic progression and functional impairment [80–83, 85].

TABLE 4 Key observational studies in systemic sclerosis (SSc) patients with mean pulmonary arterial pressure (mPAP) 21–24 mmHg

First author [ref.]	Year	Patients n	PVR	Key findings
Bae [80]#	2012	28	2.6±1.4 WU	206 patients from the PHAROS registry (35 mPAP ⩽20 mmHg, 28 mPAP 21–24 mmHg, 143 PH with mPAP ⩾25 mmHg) 55% 21–24 mmHg group developed PH (mean follow-up 26 months) 88% 21–24 mmHg group also had an increase in mPAP at exercise which fulfilled the 3rd WSPH criteria for PH-exercise
Valerio [81]#	2013	86	2.3±0.9 WU	228 SSc patients (86 mPAP 21–24 mmHg, 142 mPAP ⩽20 mmHg) 19% 21–24 mmHg group developed PAH (mean follow-up 45 months) In addition, 1 patient developed PH-LHD and 1 patient PH-lung mPAP 21–24 mmHg (HR 3.7) and TPG ⩾11 mmHg (HR 7.9) predicted development of PAH (both p<0.001)
Visovatti [82]#	2014	36	2.3±0.7 WU	Post-hoc analysis of 244 SSc patients from the DETECT study cohort: 60% mPAP ⩽20 mmHg, 15% mPAP 21–24 mmHg and 25% PAH Compared with mPAP ⩽20 mmHg, mPAP 21–24 mmHg associated with higher NT-proBNP, more frequent peripheral oedema and larger left atria
Coghlan [83]#	2018	21	2.4±0.8 WU	71 patients from the DETECT study cohort with baseline mPAP <25 mmHg (50 mPAP ⩽20 mmHg, 21 with 21–24 mmHg) had repeat RHC after a median of 3 years 21–24 mmHg group had lower baseline 6MWD 33.3% 21–24 mmHg group and 22% of mPAP ⩽20 mmHg developed PAH (p=0.026) Higher PVR, TRV, IVC diameter and lower K_{CO} were predictive of subsequent PH development
Hoffmann-Vold [73]#	2018	39	Unknown	Efficacy of the DETECT protocol (n=77) compared with an earlier approach involving symptoms, D_{LCO}, NT-proBNP and sPAP estimated at echocardiography (n=84) No difference in the incidence of PAH identified using either approach DETECT approach identified more patients with mPAP 21–24 mmHg (31% *versus* 17%)
Nagel [84]	2019	14	2.3±0.4 WU	Compared with 72 patients with mPAP ⩽20 mmHg, 21–24 mmHg group had lower 6MWD (396±87 m *versus* 474±79 m, p=0.008)
Xanthouli [76]	2019	28	2.5±0.4 WU	Compared with 123 patients with mPAP ⩽20 mmHg, 21–24 mmHg group had lower 6MWD (414±100 m *versus* 488±101 m, p<0.001) and TAPSE (21±6 mm *versus* 24 ±4 mm, p=0.004)

PVR: pulmonary vascular resistance; WU: Wood Units; PH: pulmonary hypertension; WSPH: World Symposium on Pulmonary Hypertension; LHD: left heart disease; TPG: transpulmonary gradient; PAH: pulmonary arterial hypertension; NT-proBNP: N-terminal pro-brain natriuretic peptide; RHC: right heart catheterisation; 6MWD: 6-min walk distance; TRV: tricuspid regurgitation velocity; IVC: inspiratory vital capacity; K_{CO}: transfer coefficient of the lung for carbon monoxide; D_{LCO}: diffusing capacity of the lung for carbon monoxide; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion. #: published prior to the change in haemodynamic definition at the 6th WSPH.

Summary

Patients with mPAP 21–24 mmHg are at risk of developing mPAP ⩾25 mmHg during follow-up. When compared with either the previous approach (mPAP ⩾25 mmHg and PVR ⩾3 WU) or the sixth WSPH approach (mPAP >20 mmHg and PVR ⩾3 WU), the use of an mPAP threshold of >20 mmHg and a PVR threshold of ⩾2 WU is likely to be a superior approach for identifying SSc patients with pulmonary vascular disease.

SSc-PH-exercise

An excessive increase in mPAP following increased pulmonary blood flow on exercise may result from several factors including increased PVR due to pulmonary vascular remodelling, obstruction or destruction, reduced pulmonary arterial distensibility or transmission of increased left atrial pressure due to LHD [26, 86–88]. The first WSPH report stated that "some forms of pulmonary hypertension are latent and become apparent only when there is an increase in blood flow" [14]. It commented that mPAP rarely exceeds 30 mmHg on exercise, although it also subsequently stated that mPAP can increase to >30 mmHg during exercise in athletes or in the elderly [14]. As noted above, the diagnosis of exercise PH was introduced at the third WSPH in 2003 but, following a systematic review including data from 1187 healthy volunteers, it became apparent that the normal pressure response to exercise varies with age and exercise level and so defining an abnormal response by pressure alone was not possible [6]. The diagnosis of exercise PH was therefore removed at the fourth WSPH [17]. More recently, Herve *et al.* [89] studied 169 patients with resting mPAP ⩽20 mmHg who underwent exercise-RHC. The addition of a total pulmonary resistance (TPR=mPAP/cardiac output) at maximal exercise of >3 WU to the previous criteria of mPAP >30 mmHg increased the specificity in identifying patients with pulmonary vascular disease or LHD from 0.77 to 1.0 [89].

The ERS statement on pulmonary haemodynamics on exercise consequently suggested that "exercise pulmonary hypertension may be defined as the presence of resting mPAP <25 mmHg and mPAP >30 mmHg during exercise with total pulmonary resistance >3 WU" [86]. The sixth WSPH, however, did not recommend the return of a formal exercise PH diagnosis, citing the difficulty in distinguishing exercise-related changes due to pulmonary vascular disease from those due to exercise-related increases in PAWP, especially given the practical difficulties in measuring PAWP on exercise and the uncertainty regarding normal values [5].

A number of studies have investigated the prevalence of SSc-PH-exercise with estimates ranging between 7% and 48%. In the majority of studies, however, exercise echocardiography rather than RHC was employed and so the true prevalence is not known. Condliffe *et al.* [90] identified 42 patients in the UK who met the third WSPH definition of SSc-PH-exercise and observed that 18% of patients developed resting SSc-PAH during a mean follow-up of 2.3 years. Stamm *et al.* [91] studied 28 SSc-PH-exercise patients and noted that mean survival (5.2 years) was similar to that of 17 patients with SSc-PH at rest (4.4 years). Zeder *et al.* [92] recently studied 80 SSc patients with a resting mPAP <25 mmHg and observed that TPR and PVR at exercise, but not at rest, predicted subsequent survival.

Summary

Exercise haemodynamics provide an opportunity to identify latent pulmonary vascular disease. At exercise, a mPAP >30 mmHg plus a TPR >3 WU identifies patients with pulmonary vascular or left heart disease. Technical difficulties in measuring PAWP and uncertainty regarding its normal value on exercise mean that distinguishing between these states is currently difficult.

Therapy in patients with mPAP 21–24 mmHg and SSc-PH-exercise

There are limited data on the effects of PAH-specific therapies in patients with mPAP 21–24 mmHg or SSc-PH-exercise. Kovacs *et al.* [93] studied 10 patients with mPAP 21–24 mmHg (PVR 2±0.8 WU) who underwent RHC at baseline, 1-year follow-up and after 6 months of treatment with bosentan. Pulmonary artery pressures worsened during the first year of observation but were then noted to stabilise during the 6 months of therapy while PVR worsened during the observation period but then significantly improved following therapy [93]. Saggar *et al.* [94] studied 12 patients with SSc-PH-exercise and noted significant improvements in both resting and exercise haemodyamics and 6MWD after 6 months of ambrisentan. Pan *et al.* [95] randomised 38 patients with mPAP 21–24 mmHg or SSc-PH-exercise to 6 months of ambrisentan or placebo. Although there was no significant effect on mPAP, ambrisentan was associated with significant improvements in PVR and cardiac index and a trend towards improved 6MWD.

Summary

Adequately powered RCTs of PAH therapies involving SSc patients with mPAP 21–24 mmHg and PH-exercise are required.

SSc-PVOD

Pulmonary veno-occlusive disease is a rare form of PH with significant involvement of pulmonary venules and veins [96]. The incidence of idiopathic disease is 0.5 per million per year [96, 97]. It can be autosomal recessively transmitted due to mutations in the *EIF2AK4* gene [98]. It can also develop following exposure to alkylating chemotherapy agents or organic solvents [99, 100]. An association with SSc has also been recognised [11, 40, 101]. It is characterised histologically by occlusive venous intimal fibrous thickening [102]. Alveolar capillaries are often dilated due to downstream obstruction and angioproliferative lesions identical to those seen in pulmonary capillary haemangiomatosis are present in the majority of cases [103]. Pulmonary arterial involvement with intimal fibrosis and medial hypertrophy may also be present, although plexiform lesions are not seen. In the second WSPH, PVOD was classified as pulmonary venous hypertension (group 2.4). Since pulmonary haemodynamics are indistinguishable from those seen in PAH, PVOD was moved into group 1 disease (1.4.1) in the third WSPH [16]. A separate grouping of 1′ was devised for the fourth WSPH [17]. In recognition of the fact that PVOD can involve the pulmonary arterial, capillary and venous bed, the sixth WSPH defined a new classification (1.6): PAH with overt features of venous/capillaries (PVOD/PCH) involvement [5]. PVOD is characterised at lung function testing by significantly reduced D_{LCO} and radiologically by septal lines, centrilobular ground-glass changes and mediastinal lymphadenopathy [10].

Günther *et al.* [10] reviewed high-resolution computed tomography (HRCT) images for 26 SSc patients with pre-capillary PH and reported septal lines in 89%, centrilobular ground-glass opacities in 46% and mediastinal lymphadenopathy in 58%. The presence of ⩾2 radiographic signs was associated with subsequent pulmonary oedema following commencement of PAH-specific therapy. Dorfmüller *et al.* [11]

compared tissue samples from eight patients with CTD-PAH to samples from 29 IPAH patients. Pulmonary vein and venule obstructive lesions were present in 75% of CTD-PAH patients but only 17% of the IPAH group [11]. In addition, 50% of the CTD patients had developed pulmonary oedema following commencement of PAH-specific therapy. Gupta *et al.* [104] recently reported features of PVOD in 15 out of 18 patients with SSc-PH-ILD who had undergone lung transplantation. It must be noted that the incidence of pulmonary oedema in these studies was significantly higher than is seen in routine clinical practice and that extrapolating the high incidences of PVOD observed in highly selected histopathological studies to the general SSc population is difficult. Nevertheless, PVOD should be considered if clinical deterioration occurs following commencement of PAH-specific therapy in patients with SSc. Survival in PVOD is poor and early transplant referral in suitable patients is recommended [105–107].

Summary

SSc is not only associated with the development of overt PVOD but it is likely that a proportion of patients with SSc-PAH have a PVOD component to their disease.

SSc-PH-LHD

Primary cardiac involvement in SSc may involve the myocardium, pericardium, conduction system and valves, with estimates of overall prevalence of clinically overt disease of 7–39% [108, 109]. Myocardial involvement may result from fibrosis or microvascular disease [110, 111] while LHD may also develop due to comorbidities such as systemic hypertension and coronary arterial disease. De Luca *et al.* [112] demonstrated greater levels of fibrosis at endomyocardial biopsy and a greater tendency of heart failure in 12 patients with SSc-associated myocarditis compared with 12 patients with idiopathic myocarditis and 10 patients with myocarditis associated with other forms of autoimmune disease. Cardiac magnetic resonance imaging (MRI) may demonstrate myocardial abnormalities even in the absence of overt cardiac dysfunction. For example, Poindron *et al.* [113] identified evidence of diffuse myocardial fibrosis using T1 mapping at cardiac MRI in 36 out of 72 unselected SSc patients, despite there being no difference in right or left ventricular volumes or ejection fraction between those with or without elevated T1. Ntusi *et al.* [114] demonstrated increased focal myocardial fibrosis (late gadolinium enhancement) and mycocardial oedema (using T2 mapping) in addition to higher T1 levels in 19 SSc patients compared with 20 controls. Although biventricular size and global ventricular function were preserved, impairment of peak systolic circumferential strain and peak diastolic strain rate, which correlated inversely with the level of diffuse myocardial fibrosis, were observed in the SSc group. Using echocardiography, Tennøe *et al.* [115] observed left ventricular diastolic dysfunction in 17% of 275 SSc patients at baseline and in 29% of patients after a median of 3.4 years follow-up. Allanore *et al.* [116] identified reduced left ventricular systolic function at echocardiography in 5.4% of 7073 patients in the European Scleroderma Trials and Research Group database. Patients without evidence of left ventricular dysfunction using standard echocardiography may have evidence of early "sub-clinical" disease using newer techniques. Guerra *et al.* [117] compared global longitudinal strain by performing speckle tracking echocardiography in 52 SSc patients without PH or known LHD and 52 age-matched controls. They observed a 2.5-fold increased risk of subclinical left ventricular systolic impairment and a 3.3-fold increased risk of subclinical right ventricular systolic impairment. D'Alto *et al.* [118] recently compared the response to fluid challenge in 25 SSc patients without PH and 25 healthy controls and concluded that SSc patients have an increased frequency of subclinical LV diastolic dysfunction.

Patients diagnosed with SSc-PAH may have co-existing LHD or occult PH-LHD. Fisher *et al.* [35] demonstrated LV diastolic dysfunction in 33% of patients who fulfilled haemodynamic diagnostic criteria for SSc-PAH but in only 10% of patients diagnosed with IPAH. Fox *et al.* [119] reclassified 11 (48%) out of 29 SSc-PAH patients with PH-LHD following a fluid challenge; mean left atrial dimension was higher in the reclassified patients. Robbins *et al.* [120] subsequently performed a fluid challenge in 207 patients (49% with an underlying CTD) who met haemodynamic diagnostic criteria for PAH. 46 patients (22%) were reclassified with PH-LHD; body mass index was higher and there was a higher frequency of systemic hypertension, diabetes and left atrial enlargement when compared with those patients who were not reclassified [120].

Differentiating between SSc-PAH and SSc-PH-LHD purely on the basis of haemodynamics may be problematic given the difficulties that can be experienced in obtaining reliable PAWP measurements. Lammi *et al.* [121] observed that 30% of 120 patients in the PHAROS registry with repeat RHC changed their PH classification group at follow-up. Patients' pre-test probability for SSc-PAH or SSc-PH-LHD should therefore be assessed by considering risk factors (such as systemic hypertension, obesity and diabetes), ECG, left atrial size and markers of diastolic dysfunction on echocardiography [103]. It is

recommended that PAWP is measured at end-expiration and that blood oxygen saturation in the wedged position should be checked to ensure that a reliable wedged position has been achieved [122].

PH-LHD may exist as a purely passive process whereby increased left ventricular filling pressures are transmitted backwards through the pulmonary circulation [21]. The fifth WSPH introduced the term isolated post-capillary PH (table 1) to describe the clinical state which is currently defined as mPAP >20 mmHg, PAWP >15 mmHg and PVR <3 WU (table 2) [21]. In some patients with PH-LHD, however, processes such as increased endothelin-1, inflammatory cellular infiltrate and reduced nitric oxide-induced vasodilation, can result in the development of an additional pulmonary vasculopathy [21]. These patients develop an increased PVR and are more likely to have features of PAH such as severely elevated mPAP and significant RV dilatation and dysfunction [123]. This state is termed combined pre- and post-capillary PH (CpcPH) and is defined as mPAP >20 mmHg, PAWP >15 mmHg and PVR ⩾3 WU [21]. Patients with CpcPH typically also have an elevated transpulmonary gradient (TPG=mPAP–PAWP) >12 mmHg and a diastolic pulmonary artery pressure to PAWP gradient ⩾7 mmHg.

20% of patients with SSc-PH in a large multicentre cohort were diagnosed with SSc-PH-LHD [27]. The commonest form of SSc-PH-LHD is that associated with heart failure with preserved ejection fraction (SSc-PH-HFpEF). Bourji *et al.* [124] compared 93 SSc-PAH patients with 24 SSc-PH-HFpEF patients. Patients with SSc-PH-HFpEF had higher body mass index, mPAP and PAWP and larger left atria but similar TPG to patients with SSc-PAH. Survival in SSc-HFpEF, when adjusted for haemodynamics, was inferior [124].

A number of RCTs have assessed the role of PAH-specific therapies in patients with PH-LHD [125–128]. Apart from a small study by Guazzi *et al.* [126] involving 44 patients treated with sildenafil which reported improvements in PVR and cardiopulmonary exercise test parameters, the published studies, to date, have failed to reach their primary end-points. Only one of these studies, the MELODY-1 trial, enrolled patients with CpcPH. There are a lack of data assessing response to PAH-specific therapies in SSc-PH-LHD.

Summary

The incidence of subclinical and overt LHD is increased in patients with SSc. A fluid challenge should be considered in patients with an increased pre-test probability of PH-LHD who have a PAWP of 13–15 mmHg. Treatment of underlying LHD should be optimised. Further data are needed regarding response to PAH therapies, especially in patients with SSc-CpcPH.

SSc-PH-ILD

Interstitial changes are visible on HRCT in up to 80% of SSc patients while clinically overt ILD is present in up to 40% [129]. The majority of SSc patients with ILD have nonspecific interstitial pneumonia with usual interstitial pneumonia being present in <10% of cases [130–132]. SSc-ILD is more common in DcSSc, in older patients at disease onset and in black and male patients [133–135]. Typically, ILD occurs within the first 3 years from diagnosis in DcSSc [135] while it develops later in LcSSc [136]. Goh *et al.* [137] observed poorer outcomes in SSc patients with extensive disease (defined as >20% lung involvement on HRCT or forced vital capacity (FVC) <70% in indeterminate cases) as opposed to limited disease. There are, however, no data validating the optimal threshold of lung involvement to differentiate SSc-PH-ILD from SSc-PAH. Some studies of SSc-PH-ILD have adopted the system of Goh *et al.* [137] while other studies have used a range of criteria including: the presence of any ILD [129, 138]; fibrosis extent >5% plus total lung capacity (TLC) or FVC <70% [139]; TLC <70% or moderate-severe fibrosis plus TLC 60–70% [140]; fibrosis extent >33% or FVC <60% [90]. Launay *et al.* [141] also used the system of Goh *et al.* [137] during their cluster analysis of 200 SSc patients with pre-capillary PH. In this study the presence of extensive ILD (cluster 2) was associated with significantly poorer survival while the presence or absence of limited ILD in the other three clusters did not appear to have prognostic importance. Antoniou *et al.* [142] identified combined fibrosis and emphysema in 12% of SSc patients with ILD including in 7.5% of life-long nonsmokers. Combined fibrosis and emphysema is associated with an increased risk of PH. Cottin *et al.* [143] demonstrated PH in five out of 10 SSc patients with combined fibrosis and emphysema.

Several studies have reported poorer survival in patients with SSc-PH-ILD compared with SSc-PAH [90, 138–140]. Meta-analysis in 2013 demonstrated 3-year survival of 56% in SSc-PAH and 35% in SSc-PH-ILD [9]. In a study of 39 SSc-PAH and 20 SSc-PH-ILD patients, Mathai *et al.* [140] found independent prognostic factors to be a diagnosis of SSc-PH-ILD, the presence of DcSSc, PVR index and D_{LCO}. Similarly, Chauvelot *et al.* [138] observed that the presence of ILD, together with chronic kidney

disease and a lower 6MWD, was an independent prognostic factor in a study involving 68 SSc-PH-ILD and 62 SSc-PAH patients. Response to PAH-specific therapies appears to be reduced in patients with SSc-PH-ILD. Le Pavec *et al.* [144] studied 70 patients with SSc-PH-ILD and demonstrated no improvements in WHO FC, 6MWD or pulmonary haemodynamics following institution of PAH therapies. Chauvelot *et al.* [138] observed poorer survival and lower frequency of improvement in WHO FC in SSc-PH-ILD compared with SSc-PAH patients.

Previous RCTs of PAH therapies in patients with non-CTD associated ILD±PH have either been negative [145] or associated with adverse outcomes [146, 147]. However, Waxman *et al.* [148] recently published the results of the INCREASE study which included 72 PH patients with CTD-associated ILD (CTD-PH-ILD) who were randomised to nebulised treprostinil or placebo for 16 weeks. Receiving treprostinil was associated with significant benefits in NT-proBNP and clinical deterioration (both $p<0.05$) while there was an improvement in 6MWD of 44 m in the CTD-ILD-PH patients (95% CI 10.77). There was, however, no effect of therapy on quality of life.

Summary

Survival in SSc-PH-ILD is worse than in SSc-PAH. Most observational studies have reported a lack of functional and haemodynamic response to PAH therapies in patients with SSc-PH-ILD. Further RCTs of PAH therapies specifically in SSc-PH-ILD are needed.

Conclusion

Several different and overlapping forms of PH can present in patients with SSc. Accurate and early diagnosis to allow optimal treatment is therefore essential. Therapeutic uncertainty exists for SSc-PAH patients with mild pulmonary haemodynamics, SSc-PH-LHD or SSc-PH-ILD and further studies in these groups are urgently needed. Furthermore, the optimal PVR threshold for diagnosing PAH and the role of exercise in identifying early disease requires further elucidation.

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