Pulmonary Circulation on the Crossroads Between the Left and Right Heart in Systemic Sclerosis

A Clinical Challenge for Cardiologists and Rheumatologists

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KEYWORDS

• Pulmonary hypertension • Systemic sclerosis • Right heart • Pulmonary circulation

KEY POINTS

- Pulmonary hypertension is frequent in systemic sclerosis and is associated with poor prognosis.
- Pulmonary hypertension occurs as a result of a pulmonary arteriopathy but also can be a consequence of interstitial lung disease and/or left heart involvement.
- These phenotypes may be difficult to differentiate and often overlap, complicating both the diagnosis and the follow-up.
- An integrated multidisciplinary approach, including a rheumatologist, cardiologist, and pulmonologist, is mandatory to improve patients' management.

INTRODUCTION

Systemic sclerosis (SSc) is a complex multiorgan immune-mediated disease characterized by fibrosis of the skin and internal organs and by vasculopathy.[1,2] Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mm Hg at rest, as assessed by right heart catheterization

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(RHC).[3] In patients with SSc, PH can be the result of an isolated pulmonary arteriopathy, determining a condition of pulmonary arterial hypertension (PAH), a relevant cause of morbidity in SSc.[4] It is included in the first group of the new clinical classification of PH, characterized by precapillary PH with pulmonary artery wedge pressure (PAWP) less than or equal to 15 mm Hg.[3]

Elevated pulmonary artery pressure (PAP) in SSc also may occur, however, as a consequence of interstitial lung disease (ILD) or left ventricular (LV) systolic and/or diastolic dysfunction.[5] In these situations, the term PAH is not correct and the more generic term PH should be used. It is also true that an overlap between the different etiologies of PH is possible and likely frequent in SSc patients; therefore, it is important to distinguish the hemodynamic contribution of the diverse mechanisms, which are linked to different therapeutic and prognostic correlates.

DIFFERENT ETIOLOGIES OF PULMONARY HYPERTENSION IN SYSTEMIC SCLEROSIS

The pathophysiology of the mechanisms leading to the onset of PH is complex, with interplay between inflammation process, autoimmunity, and systemic vasculopathy. Some overlap within different subtypes of PH may exist, because this condition shows a pathophysiologic continuum,[6] which is particularly evident in SSc patients, who can present with several forms of PH during the course of the disease. The most typical form was traditionally believed PAH, group I, according to the most recent European and American guidelines.[3,7] Group II (PH due to left heart disease) and group III (PH due to lung disease and/or hypoxia), however, also can be present in SSc patients. In the Pulmonary Hypertension Assessment of Recognition of Outcomes Registry of Scleroderma (PHAROS), SSc patients with PH were classified as group I PAH in 69% of cases, group II PH in 10% of cases, and group III PH in 21% of patients.[8] Rarely, pulmonary veno-occlusive disease (PVOD) may also be present in SSc patients.[9]

Pulmonary Arterial Hypertension

According to the 2015 European Guidelines[3] on PH, PAH is defined by a mean PAP (mPAP) of greater than or equal to 25 mm Hg with a PAWP of less than or equal to 15 mm Hg at RHC and a pulmonary vascular resistance (PVR) of greater than 3 Wood units with either normal or reduced cardiac output (CO)[10] in absence of other forms of precapillary PH. The prevalence of PAH in SSc is reported as 8% to 12% in the European League Against Rheumatism (EULAR) Scleroderma Trials and Research Group database.[2] Nevertheless, a recent study confirms a lower prevalence of PH in Italy compared with Anglo-Saxon cohorts.[11] Moreover, it ranges from 0.5% to 15% based on RHC diagnosis in different studies.[12–14] PAH greatly affects morbidity and mortality in these patients, responsible for almost 30% of SSc-related deaths.[2] SSc patients with PAH have a significantly worse 3-year survival compared with SSc patients without PAH.[15] It is debated whether SSc-PAH is less responsive to specific vasoactive therapies than patients with idiopathic PAH,[16–18] because data from randomized trials indicate that more intensive treatments—especially combination therapy—would gain similar benefits in SSc-associated PAH compared with other forms of PAH.[19–23] One of the reasons given to explain the suboptimal efficacy of PAH treatment, highlighted in some studies, is that drugs are started too late in the course of the disease, due to delay in diagnosis. Signs and symptoms of PAH are generally nonspecific and underestimated, because they are often not discriminated from general SSc symptoms, postponing the diagnosis to more advanced phases of the disease, characterized by structural and irreversible damage of the pulmonary vasculature. It has been shown that patients identified with PAH via an active screening program have a better prognosis than those diagnosed in the course of routine clinical practice,[24] underlining the potential benefit of early diagnosis and early intervention in the course of the pathologic process.

PVOD is a rare form of PH, with a prevalence of 0.1 to 0.2 per million persons per year. From a histologic point of view it is characterized by fibrotic occlusion of postcapillary venules. In the 2015 European Society of Cardiology Guidelines[3], PVOD has been classified, together with pulmonary capillary hemangiomatosis, in a specific subgroup next to PAH, because of the similar pathologic, genetic and clinical features.[3] PVOD may complicate SSc,[25,26] although a recent study showed that radiological signs of PVOD seem less common in SSc-PAH than previous reports suggest. They correlate, however, with a worse prognosis, and clinicians should be aware of the risk of noncardiogenic pulmonary edema induced by PAH-specific therapy.[9] Portal hypertension can also occur in patients with hepatobiliary involvement, which is not infrequent in SSc.[5,27]

Pulmonary Hypertension Due to Lung Disease

ILD is common in both diffuse and limited cutaneous SSc, with clinical manifestations in approximately 40% of patients.[28] When ILD is

complicated by PH, the prognosis of patients worsens significantly.[15,29–31] Mathai and colleagues[30] showed that PH associated with ILD (PH-ILD) in SSc patients was linked to a 5-fold increased risk of death compared with SSc-PAH. These data were confirmed in another recent large study by Condliffe and colleagues,[15] where the 3-year survival was shown significantly worse in SSc patients with PH-ILD, compared with patients with isolated SSc-PAH. The pathogenic basis of PH-ILD is multifactorial, including fibrotic destruction of the pulmonary vasculature and parenchyma, vascular remodeling due to chronic hypoxia, and diffuse specific vasculopathy similarly to that observed in isolated SSc-PAH.[31,32]

An article by Launay and colleagues[33] published in 2011 shed some light on the clinical and prognostic characteristics of PH-ILD in SSc. Patients with PH-ILD were more likely to be younger male patients, with the diffuse cutaneous form of the disease, more frequent with antitopoisomerase, and less frequent anticentromere antibodies, with a lower Pa_{O_2} and a worse prognosis compared with SSc-PAH. Pericardial effusion and diffusion capacity for carbon monoxide (DLCO), with a cutoff of 30%, were the only 2 prognostic determinants in the PH-ILD group, whereas mPAP was not, consistent with previous data.[30] Usually, in patients with COPD or ILD unrelated to SSc, PH is generally mild, and when mPAP is greater than 35 mm Hg, it is considered too high to be entirely due to ILD. The prognosis for patients with mild PH-ILD in this study was as poor as for patients with moderate to severe PH-ILD.[33] Because SSc is frequently associated with ILD, in a patient with SSc with both PH and ILD, it can be difficult to firmly establish whether the patient has a PAH independent from ILD, a PH-ILD, or the combination of PH-ILD and a pulmonary vasculopathy (**Fig. 1**).

Combined pulmonary fibrosis and emphysema syndrome (CPFE) can also be a cause of PH in SSc[34] and is associated with poor prognosis. It is characterized by combined emphysema of the upper lobes and fibrosis of the lower lobes on chest CT, with preserved lung volumes, impaired DLCO, and hypoxemia at exercise and at rest in advanced cases. Whereas in the general population CPFE is usually observed in smokers, in SSc patients this condition is also present in nonsmokers.[35]

Pulmonary Hypertension Due to Left Heart Disease

Cardiac involvement in SSc is frequent and relevant from a prognostic point of view.[36] Although the real incidence is highly variable because it depends on the definition of cardiac involvement and on the diagnostic tools used to detect it, cardiac magnetic resonance[37,38] and autoptic studies[39] report percentages up to 75%. Therefore, it is difficult to exclude patients with any kind of left heart abnormality when assessing PH in SSc.[40]

In a retrospective population of 107 SSc patients, Fox and colleagues[41] evaluated all subjects with suspected PH by right and left heart catheterization, assessing LV end-diastolic pressure (LVEDP) measurement prefluid and postfluid challenge. The study found a high prevalence of postcapillary

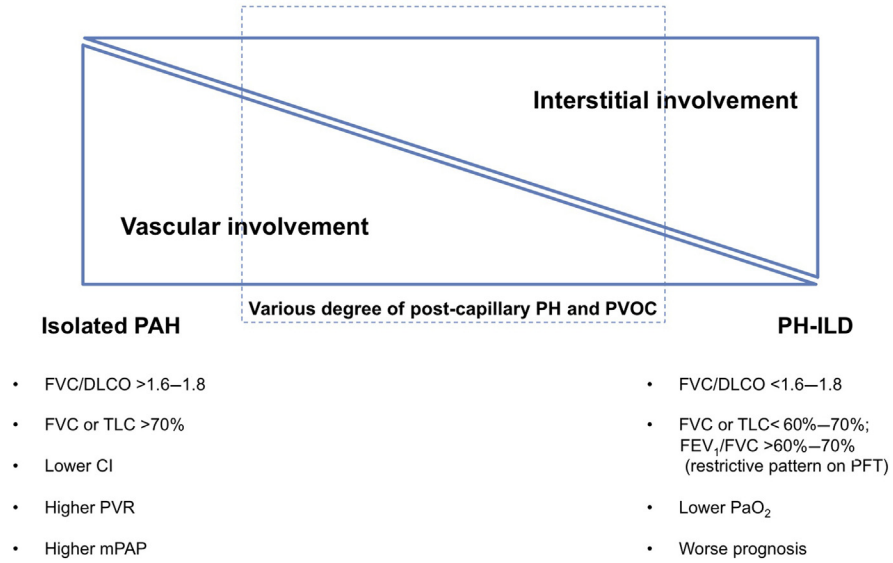


Fig. 1. The spectrum of PH phenotype in SSc patients. CI, cardiac index; FEV_1, forced expiratory volume in 1 second; Pa_{O_2}, partial pressure of O_2 in arterial blood; TLC, total lung capacity.

PH in this population (mPAP ≥25 mm Hg, PAWP >15 mm Hg, and normal or reduced CO), including a significant number of occult postcapillary PH (mPAP ≥25 mm Hg, PAWP ≤15 mm Hg, LVEDP >15 mm Hg before or after a 500-mL fluid challenge administered over 5–10 min). Although RHC is the gold standard for assessment of intracardiac and pulmonary pressures, some controversial issues remain. In a large cohort of 11,523 patients undergoing simultaneous right heart and left heart catheterization, Halpern and Taichman[42] found a high percentage of patients with a significant discrepancy between PAWP and LVEDP (PAWP <15 mm Hg and LVEDP >15 mm Hg). Therefore, approximately half of the patients presumed to have PAH based on PAWP were found to have postcapillary PH based on LVEDP. It is known that PAWP and LVEDP are not identical: a compliant left atrium can protect the pulmonary vasculature from elevated LVEDP, whereas a stiff left atrium can result in postcapillary PH in the setting of a normal LVEDP.[40,43] Moreover, filling pressures vary over time, as shown in the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) database, where 10% of patients with an initial PAWP less than or equal to 12 mm Hg had a follow-up PAWP of greater than or equal to 16 mm Hg, whereas 50% of patients with an initial PAWP greater than or equal to 16 mm Hg had a follow-up PAWP less than or equal to 12 mm Hg.[44] Altogether, these data highlight the discrepancies that may occur between PAWP and LVEDP, which reflect the complexity of diagnosing pulmonary vascular disease in the presence of left heart abnormalities[40]; a significant overlap between PAH and PH due to left heart disease—which is frequent in SSc—makes a straightforward differentiation between the 2 conditions not always feasible[6] and the management uncertain.

THE NEED FOR EARLY DIAGNOSIS—A MULTIPARAMETRIC APPROACH

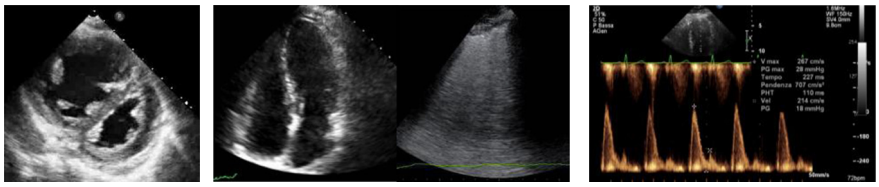
Many attempts have been made in the past few years to establish a reliable way to identify the subgroup of SSc patients prone to developing PAH early, given the availability of more effective PAH-specific therapies and the evidence that patients identified early through an active screening program have better survival than patients identified during routine clinical care.[24] The European Guidelines recommend resting echocardiography as a screening test in asymptomatic SSc patients, followed by annual screening with echocardiography, DLCO, and biomarkers.[3]

Echocardiography

Echocardiography is the routine imaging tool to noninvasively assess the right heart and pulmonary circulation unit.[45] Although RHC remains the gold standard for confirming diagnosis and supporting treatment decisions, echocardiography has the advantage of being widely available, cost-effective, and well tolerated. A thorough cardiac ultrasound examination should include not only the indirect estimation of systolic PAP (sPAP), which is essential in symptomatic patients with a clinical suspicion of PH to establish the probability of this condition, but also a detailed evaluation of the right and left heart dimensions and function as well as pulmonary artery diameter and inferior vena cava size and collapsibility. It is only by an accurate description of the 4 chambers' anatomic and functional characteristics that it is possible to attempt a prediction of precapillary versus postcapillary PH[46] (**Table 1**). A careful assessment of the right heart is often neglected in routine echocardiograms, despite its relevance, not only in connective tissue disease (CTD).[45] An adequate echocardiogram should include a right ventricular (RV)-focused apical 4-chamber view, which would reduce the variability in how the right heart is sectioned and, consequently, in RV dimensions and areas.[47] For the right atrium (RA), as well for the left atrium, volumes or at least areas, are more accurate to determine the chamber size compared with linear dimensions. The European Guidelines include an end-systolic RA area greater than 18 cm^2 as one of the echocardiographic signs suggestive of PH, to be used to assess the probability of PH in addition to tricuspid regurgitation (TR) velocity.[3] The acceleration time (ACT) of the RV outflow tract (RVOT) is another simple measurement that should be assessed: when less than 105 milliseconds and/or showing a midsystolic notch in the Doppler profile, it is considered a suggestive sign of PH,[3] as an indirect marker of increased PVR.[48,49]

It is now well established that there is a poor RV adaptation to overload in SSc compared with other CTDs,[50] which is also linked to a complex physiopathology with possible diastolic and/or systolic dysfunction. Huez and colleagues[51] pointed out RV diastolic dysfunction in SSc patients as well as a decrease in pulmonary arterial compliance. Overbeek and colleagues[52] showed that for the same level of PAP, SSc patients had lower RV systolic function compared with patients with idiopathic PAH; they also demonstrated that the RV systolic response to an increase in PAP was poorest in SSc patients. These studies highlight the importance of assessing RV systolic function in SSc patients, which unfortunately is often missing in

Table 1
Typical echocardiographic features in different pulmonary hypertension phenotypes in systemic sclerosis



	Pulmonary Arterial Hypertension	Interstitial Lung Disease	Left Cardiac Involvement
LV dimensions	Normal to reduced	Usually normal	Usually increased
Left atrial dimensions	Normal	Normal	Usually increased
RV-RA dimensions	Increased	Normal/increased	Normal
Eccentricity index	≥1–2	Usually <1.2	≤1
LV systolic function	Normal	Normal	Reduced (ejection fraction can be normal until later stages)
LV diastolic function	Normal, grade I E/e' usually <10	Normal, grade I E/e' usually <10	Grade II–-III E/e' usually >10
RV function	Reduced	Usually normal	Usually normal (reduced in biventricular involvement)
Mitral regurgitation	Trivial–mild	Trivial–mild	Mild–moderate
TR	Moderate–severe	Mild–moderate	Usually mild
sPAP	+++	++	+
Inferior vena cava	Dilated and fixed	Usually normal and collapsible	Normal and collapsible
PVR	+++	+/++	Normal
Other signs	• RV forming heart apex • Reduced ACT ± notch of RVOT Doppler spectrum • Pericardial effusion	Multiple diffuse B lines with irregular pleural line at lung ultrasound	Pericardial effusion

Abbreviations: E/e', early mitral inflow velocity and mitral annular early diastolic velocity; +, slightly increased; ++, moderately increased; +++, highly increased.

echocardiographic reports.[53] Echocardiographic RV diastolic parameters can also be easily assessed[54] and have been shown significantly different compared with control subjects.[55] New techniques for the assessment of myocardial deformation have also been used to assess RV and RA function in SSc, with significant results[56–59]; however, their use in routine clinical practice is still limited.

The addition of lung ultrasound to a standard echocardiogram, adding only a few minutes to the examination, may reveal the presence of sonographic signs of pulmonary interstitial involvement (sonographic B-lines) which, when associated with an irregular pleural line, are highly suggestive for ILD and may have a role in the screening algorithm[60,61] (see **Table 1**).

Exercise Echocardiography

There is increasing awareness of the clinical relevance of an abnormal pulmonary hemodynamic response during exercise,[62] but several questions

remain to be elucidated; therefore, exercise PH is an entity that has not been endorsed by the latest European Guidelines, where its definition, even when estimated by RHC, has been considered unsupported due to insufficient data.[3] More recently, exercise PH has been defined as the presence of resting mPAP less than 25 mm Hg and mPAP greater than 30 mm Hg during exercise with total pulmonary resistance greater than 3 Wood units, during RHC.[62] Exercise PH seems to represent the hemodynamic manifestation of early pulmonary vascular disease, left heart disease, lung disease, or a combination of these conditions,[62] acting as a possible transitional phase anticipating resting PH.

Exercise echocardiography is a noninvasive tool to estimate pulmonary hemodynamics during exercise and is useful to assess abnormalities of pulmonary vascular function as well as the state of the right heart, although it does not have an established role in the management of SSc patients. A main issue in SSc is the high percentage of patients showing exercise PH during exercise stress echocardiography, which clearly overestimates the subset of SSc patients who will develop PAH.[63–66] PAP is dependent, however, not only on PVR, which is abnormally increased in PAH, but also on left atrial pressure and CO, as shown both in healthy subjects[67] and in SSc.[51] It is, therefore, crucial to define the relative hemodynamic contribution of each parameter to better understand the main determinants of increased PAP.[68,69] Exercise echocardiography may identify a subset of SSc patients without PH with an inappropriate exercise-induced increase in pulmonary arterial systolic pressure (PASP) and early signs of RV dysfunction. A study[68] enrolling 172 consecutive SSc patients in New York Heart Association class I/II showed a higher exercise-induced sPAP (36.9 ± 8.7 vs 25.9 ± 3.3 mm Hg; $P<.0001$) and a lower cardiac index increase (2.8 ± 1.2 vs 4.6 ± 2.3 L/min/m^2; $P<.0001$) than controls.

In a population of 164 SSc patients, the authors demonstrated that exercise PH (defined as an exercise sPAP $\geq$50 mm Hg and exercise PVR $\geq$3 Wood units during echocardiography) was present in approximately half of the patients with normal resting sPAP and was affected by age, ILD, and RV and LV diastolic dysfunction, whereas only a minority (5%) of these patients had an increase in PVR during exercise, suggesting high heterogeneity of the pathophysiologic background.[69] These data were further confirmed in a smaller population of 45 patients, where exercise PH was present in 21 patients, with a positive correlation between exercise sPAP and both exercise left atrial pressure and exercise PVR (respectively, $r^2 = 0.61$ and $r^2 = 0.57$; $P<.05$), again suggesting that exercise PH was related to both increased exercise LV filling pressure and exercise PVR.[70] Thereby, exercise echocardiography allows identification of those patients with an abnormal increase in PAP as well as a better understanding of the mechanism leading to abnormal pulmonary hemodynamic response during exercise.

Exercise echocardiography may also help distinguish patients at risk of developing further resting PH. Codullo and colleagues[71] found that a ΔsPAP cutoff of greater than 18 mm Hg, identified by receiver operating characteristic curve analysis, had a sensitivity of 50% and a specificity of 90% for the development of resting PH during follow-up. In another study, exercise PH has been found useful to predict the onset of resting PH at echocardiography during follow-up, in addition to nailfold videocapillaroscopy.[72] Exercise PH with normal resting sPAP was present in 43% of patients; after a mean follow-up of 24 months, 11 patients developed resting PH (as defined by echocardiography), and all of them belonged to the exercise PH group. Patients who did not have exercise PH never developed a resting sPAP greater than 35 mm Hg during the follow-up.[72]

Kusunose and colleagues[73] prospectively enrolled 78 patients with CTD (including 70% of SSc) with a baseline resting and postexercise echocardiographic evaluation. During a median follow-up of 32 months, 16 patients developed resting PAH. The slope of mPAP/CO had an incremental value over a 6-minute walking test distance to predict PH at follow-up. Even though exercise echocardiography is not included in the current recommendations for screening patients at risk of resting PH, it remains an interesting tool to assess the physiopathology of the hemodynamic behavior during stress, with a promising role in the early detection of abnormal vascular response. Moreover, an abnormal exercise-induced increase in PASP may explain an otherwise inexplicable effort dyspnea in SSc patients with normal baseline hemodynamics.

Nonechocardiographic Parameters

In the past few years, many studies have addressed the complex issue of early diagnosis in patients with SSc and in patients with CTD, underlining the importance of a multiparametric approach that should not be limited to transthoracic echocardiography as the sole instrumental examination for establishing the likelihood of developing PAH,[74] because other noninvasive screening tests, such as pulmonary function tests (PFTs),

and measurement of serum biomarkers, such as N-terminal pro brain natriuretic peptide (NT-proBNP), have been shown with PAH in SSc patients.[75–77] In particular, the Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis (DETECT) study enrolled patients with more than 3 years' disease duration from the first non–Raynaud phenomenon symptom and a predicted DLCO less than 60%, thus representing a high-risk population. This was the first study on PAH screening to undertake systematic RHC in all patients to develop an evidence-based algorithm for earlier identification of PAH in a mildly symptomatic population. In this study, 466 patients underwent noninvasive testing and RHC: results showed that 87 patients (19%) had RHC-confirmed PAH, a higher prevalence compared with previous studies.[78] The DETECT algorithm showed a significantly higher sensitivity in identifying patients with PAH, missing only 4% of patients as false negative. Longitudinal data from this cohort have demonstrated that 44% of the PAH patients who received an early diagnosis through the DETECT algorithm had disease progression during a relatively short follow-up time, again underlining the clinical relevance of early detection of PAH.[79] The DETECT algorithm has been successfully applied also to other populations of high-risk patients.[80] The DETECT algorithm, however, is not applicable to patients with a predicted DLCO greater than 60%. The PHAROS also confirmed that a low DLCO less than 55% and a high forced vital capacity % predicted to DLCO %predicted ratio (FVC/DLCO) greater than 1.6 are good screening parameters in addition to echo-derived sPAP in selecting those patients who are at risk to develop SSc-PAH.[81] More recently, a study comparing the DETECT algorithm with the screening models suggested by the 2009 and 2015 European Guidelines found that referring patients to RHC according to the DETECT algorithm yielded a high number of false-negative cases but was useful especially to identify patients with borderline PAP (mPAP 21–24 mm Hg),[82] which seems to be an intermediate stage on the continuum between normal pulmonary hemodynamics and PAH.[83,84]

Some recommendations for screening and detection of CTD-associated PAH were published in 2013, after a systematic review of the literature by an international expert panel.[74] This article contains the first evidence-based and consensus-based recommendations for screening and early detection of CTD-associated PAH with the aim of identifying patients with asymptomatic/preclinical disease and those with mild symptoms to prevent or delay progression of disease through early management. **Box 1** summarizes these general recommendations. It must be underlined that the quality of evidence, which was assessed according to the Grading of Recommendations Assessment, Development and Evaluation Working Group from very low to high, varies between the different statements.

The recommendations established specific criteria to recommend RHC in SSc and scleroderma spectrum disorders, which is advised in patients with (1) a TR jet velocity of 2.5 m/s–2.8 m/s with signs and/or symptoms consistent with PH; (2) a TR jet velocity of greater than 2.8 m/s with

Box 1
Summary of general recommendations for early detection of connective tissue disease–associated pulmonary arterial hypertension

General recommendations

- All patients with SSc should be screened for PAH.
- Patients with MCTD/CTD with scleroderma features should be screened similarly to patients with SSc.
- Screening is not recommended for asymptomatic patients with MCTD/CTD without scleroderma features.
- All patients with SSc and MCTD/CTD with scleroderma features with positive screening results should be referred for RHC.
- RHC is mandatory for diagnosis of PAH.

Initial screening evaluation

- PFT with DLCO
- Transthoracic echocardiography
- NT-proBNP
- DETECT algorithm if DLCO less than 60% and disease duration greater than 3 years

Frequency of noninvasive tests

- Transthoracic echocardiography annually as a screening test
- Transthoracic echocardiography if new signs or symptoms develop
- PFT with DLCO annually as a screening test
- PFT with DLCO if new signs or symptoms develop
- NT-proBNP if new signs or symptoms develop

Abbreviation: MCTD, mixed CTD.

Adapted from Khanna D, Gladue H, Channick R, et al. Recommendations for screening and detection of connective-tissue disease associated pulmonary arterial hypertension. Arthritis Rheum 2013;65(12):3196; with permission.

or without signs and/or symptoms of PH; (3) RA or RV enlargement (RA major dimension >53 mm and RV midcavity dimension >35 mm), irrespective of TR jet velocity (including nonmeasurable or <2.5 m/s); or (4) signs or symptoms of PH and an FVC/DLCO greater than 1.6 and/or a predicted DLCO of less than 60%, without an overt systolic dysfunction, a greater than grade I diastolic dysfunction, a greater than mild mitral or aortic valve disease, or evidence of PH. The expert panel did not recommend acute vasodilator testing during RHC as part of the evaluation of PAH. This is supported by the small number of patients in this subset with both a positive vasodilator test result (defined as a reduction in mPAP by at least 10 mm Hg to an mPAP of <40 mm Hg in the setting of a normal CO) and a long-term response to calcium-channel blockers.[3,85]

No clear recommendations are provided on borderline mean PAP (21–24 mm Hg) or on exercise PH, due to lack of long-term outcome data and variability in exercise testing.[86,87]

The role of RV and RA measurements underlines the importance of referring these patients to specialized centers, where echocardiography is performed by certified personnel, who will include a thorough evaluation of the right heart.

SUMMARY

Involvement of the right heart-pulmonary circulation system is crucial in SSc and represents a main prognostic determinant. PH may respond to multiple and partially overlapping mechanisms of precapillary and postcapillary etiologies. An early diagnosis is mandatory to improve outcomes, and a multidisciplinary and multiparametric approach is required to fully understand the diverse mechanisms leading to abnormal pulmonary hemodynamics.

Recommendations on how to screen SSc-related PAH have been established and may help clinicians in this complex management, although they are not meant to substitute a clinically driven individualized assessment of the patient.

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