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Invited Review

Screening for pulmonary arterial hypertension in systemic sclerosis: Now or never!

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Abstract

Systemic sclerosis (SSc), a chronic multisystem autoimmune disease characterized by fibrosis of the skin and internal organs and vasculopathy, has a high burden of mortality. One of the major contributors to mortality in patients with SSc is pulmonary arterial hypertension (PAH), which affects up to 10% of individuals and results in up to 15 years of life loss. Best practice recommendations are for asymptomatic patients with SSc and SSc-spectrum disorder to be screened annually for the early detection of SSc-PAH. Recently published data from large registries have shown improvements in the long-term outcomes in patients who are diagnosed with SSc-PAH because of systematic annual screening. This review will address the current clinical and research implications of the screening for the early detection of SSc-PAH.

Keywords: Scleroderma, systemic, pulmonary arterial hypertension, mass screening, diagnosis

Introduction

Systemic sclerosis (scleroderma; SSc) is a chronic multisystem autoimmune disease with significant clinical heterogeneity. Three common pathogenetic features include microvascular damage, generalized fibrosis of multiple organs, and dysregulation of innate and adaptive immunity (1).

The prevalence and incidence estimates of SSc vary internationally with higher prevalence reported in Australia, North America, and southern Europe, wherein the estimates range from 154 to 276 cases per million (2). Pulmonary arterial hypertension (PAH) in SSc occurs with an estimated prevalence of 10% and incidence of 1% per annum (3-6). Despite the availability of effective therapies, PAH and other pulmonary complications remain the leading cause of morbidity and mortality in these patients (7, 8).

Recommendations published following the 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018 suggest annual screening of asymptomatic patients with SSc and SSc-spectrum disorders. This has been shown to detect patients with more favorable risk stratification features at diagnosis with PAH and to be associated with improved survival compared to patients diagnosed by routine care (9-12).

Current screening recommendations include various strategies to screen patients, including annual echocardiography. However, echocardiography has limitations as a screening investigation because it relies on the assessment of tricuspid regurgitant (TR) jet velocity to determine the need for further investigation with right heart catheterization (RHC) for the definitive diagnosis of PAH. There is an evidence for discrepancies between the evaluation of TR velocity and right heart parameters by echocardiography compared with RHC, leading to the development of novel multidimensional screening algorithms that use echocardiography as a second-tier screening test (13-15).

Multidimensional screening algorithms using echocardiography as a second-tier investigation, such as the DETECT algorithm and the Australian Scleroderma Interest Group (ASIG) algorithm for the early detection of PAH in patients with SSc, have been developed and evaluated (16, 17). These screening algorithms also incorporate the assessment of known prognostic factors (or risk stratification factors) at the baseline, such as N-terminal probrain natriuretic peptide (NT-proBNP), and are included in the list of recommended screening modalities published following the 6th WSPH (12).

Economic analysis of the screening methods for the detection of PAH in patients with SSc was carried out in French, Australian, and Belgian cohorts, which suggests that screening programs are also cost saving (18, 19).

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This review will discuss the clinical and research implications of screening for the early detection of SSc-PAH, with reference to the recent updates on the definition of precapillary PH and their implications for the early detection of PAH.

Clinical consequences

Methods of screening

Recommendations for the methods of screening published following the 6th WSPH include annual screening for patients with SSc-spectrum disorders incorporating echocardiography, the DETECT algorithm, or analysis of the ratio of forced vital capacity (FVC) to diffusing capacity of the lung for carbon monoxide (DLCO), together with NT-proBNP level (12).

A systematic review performed by the WSPH task force prior to the publication of the updated recommendations reported that there were 3 frequently evaluated screening tools developed for patients with SSc, including the 2009 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines, the DETECT algorithm, and the ASIG algorithm, which are represented in Figures 1, 2, and 3, respectively (10, 12, 16, 20, 21).

Main Points

- Pulmonary arterial hypertension (PAH) in systemic sclerosis (scleroderma; SSc) occurs with an estimated prevalence of 10% and incidence of 1% per annum, and remains one of the leading causes of morbidity and mortality in this population.
- Early detection of PAH through the annual systematic screening of all patients with SSc and SSc-spectrum disorders is recommended following the 6th World Symposium on Pulmonary Hypertension.
- Multidimensional screening algorithms, such as the Australian Scleroderma Interest Group (ASIG) algorithm and the DETECT algorithm, include assessment of respiratory function tests and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) prior to transthoracic echocardiography (TTE), and outperform TTE alone with regard to sensitivity and specificity.
- Early diagnosis of PAH in SSc patients as a result of annual screening is associated with improved outcomes and reduced mortality.

The DETECT algorithm evaluates the results of 6 nonechocardiographic variables by nomogram to determine a referral for echocardiography in step 1, and in step 2, it determines the need for RHC by evaluating the echocardiographic features (right atrium area and TR velocity) (16). Although initially derived in an enriched cohort of patients with SSc disease duration >3 years and DLCO predicted of £60%, the DETECT algorithm has been externally validated in cohorts not meeting these criteria and compared with the 2009 ESC/ERS guidelines. There are 6 studies evaluating the DETECT algorithm in external cohorts, which demonstrate that the algorithm has a comparable performance with the 2009 ESC/ERS guidelines (17, 22-26).

The ASIG algorithm recommends respiratory function tests (RFTs) to evaluate the FVC/DLCO ratio and serum NT-proBNP annually in asymptomatic patients with SSc. If either result is positive, the algorithm advises referral for further evaluation of the presence of PH, including PAH. If the ratio of FVC% predicted to DLCO% predicted is ≥1.8 with DLCO predicted <70%, this suggests a discrepant reduction in the diffusing capacity and is a positive screen. Serum NT-proBNP ≥210 ng/L (or pg/mL) alone is also a positive screen (17). The ASIG algorithm was compared with the DETECT algorithm and the 2009 ESC/ERS guidelines in a cohort of patients with SSc who had been referred for RHC. The ASIG and DETECT algorithms were equally sensitive and were both superior to the 2009 ESC/ERS guidelines. Additionally, the ASIG algorithm outperformed the DETECT algorithm with respect to specificity (54.5% compared with 35.3%) (17).

Despite the published recommendations regarding screening, care gaps remain in practice (27). Analysis of the frequency of annual echocardiograms performed for patients enrolled in the Canadian Scleroderma Research Group after the publication of the 2009 ESC/ERS guidelines revealed that 59.4% of the patients had an echocardiogram after a 1-year follow-up (28). Similarly, a survey of rheumatologists in Australia revealed that only over half of the respondents ordered annual screening for asymptomatic patients with early SSc, and these were even lower for patients with late disease (9).

An independent evaluation of PAH screening practices by rheumatologists in Canada also included evaluation of the frequency of annual screening for dyspnea, as well as annual transthoracic echocardiography (TTE) and RFT. The authors found a discrepancy between the frequency of screening for dyspnea and ordering annual TTE and RFTs (88% of patients compared with 74% and 79%, respectively), suggesting that there are barriers to requesting these tests (29). Concerns have also been

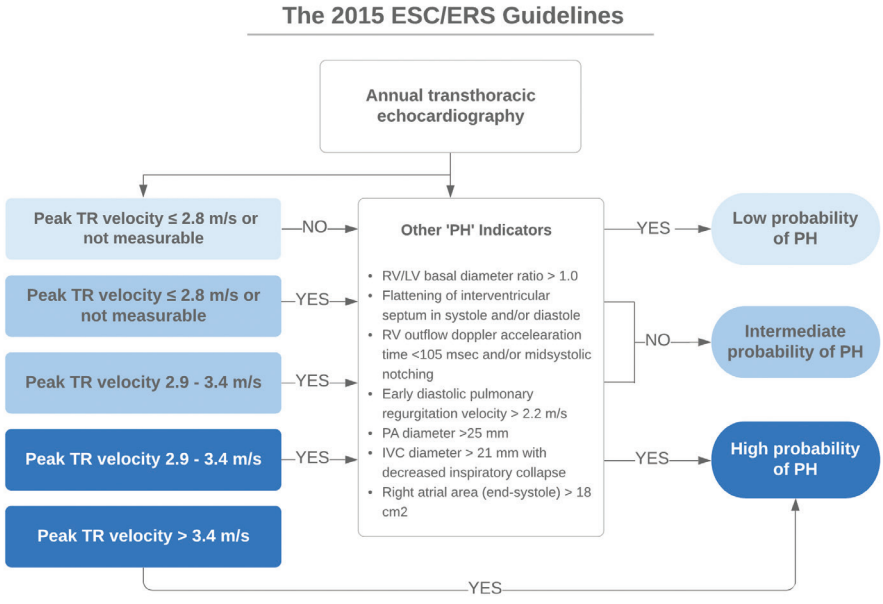

Figure 1. The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.*

*The 2015 ESC/ERS recommendations for echocardiography to be incorporated into the screening of patients with scleroderma or scleroderma-spectrum disorders (10, 12).

TR: tricuspid regurgitation; m/s: meters/second; RV/LV: right ventricle or left ventricle; PA: pulmonary artery; IVC: inferior vena cava.

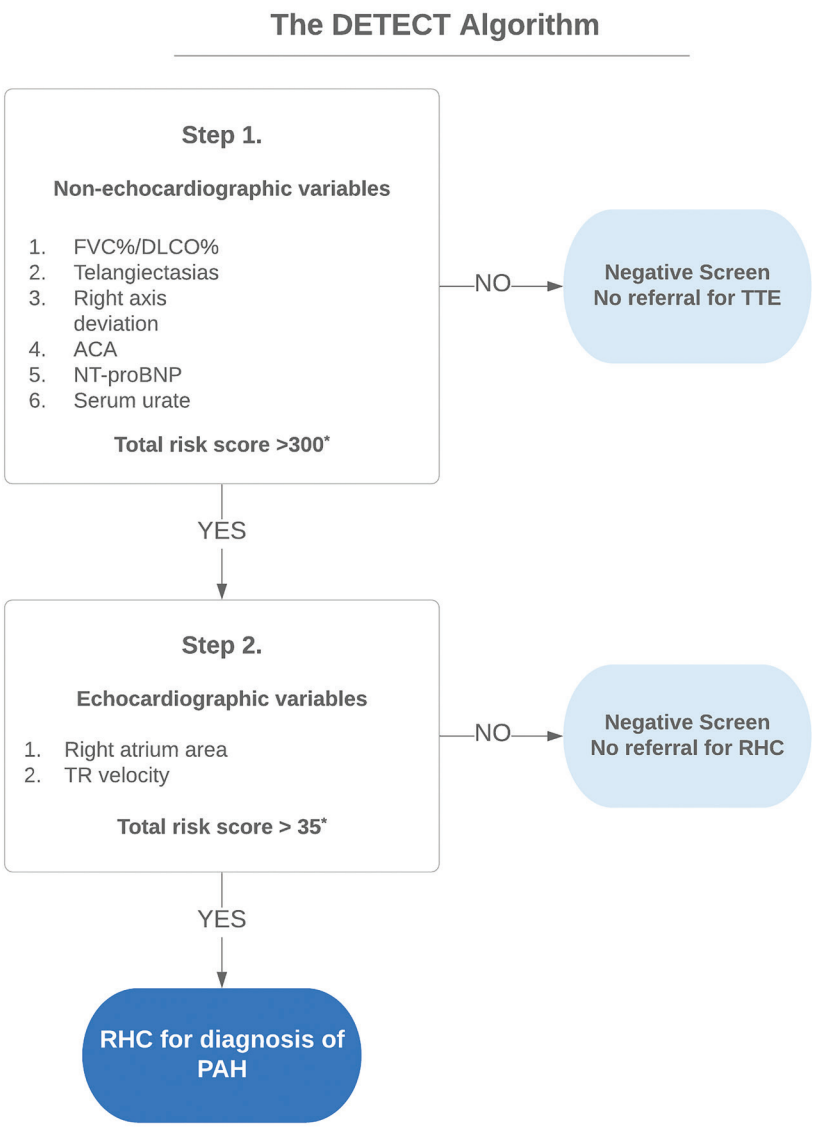

Figure 2. The DETECT algorithm.*

*The DETECT algorithm evaluates the calculated scores in two steps, the first evaluates six nonechocardiography variables to determine the need for transthoracic echocardiography (TTE) and the second evaluates two TTE variables to determine the need for right heart catheterization (RHC) (16).

FVC%: forced vital capacity % predicted; DLCO%: diffusion capacity of the lung for carbon monoxide % predicted; ACA: anticentromere antibody positivity; NT-proBNP: N-terminal probrain natriuretic peptide; TR: tricuspid regurgitation; PAH: pulmonary arterial hypertension.

raised regarding the complexity of the composite screening measures, such as the DETECT algorithm, and further evaluation of the feasibility of screening algorithms is an area for future research (30).

Long-term benefits

The most convincing evidence for the long-term benefit of screening for the early detection of SSc-PAH comes from two registries comparing the outcomes between patients whose PAH was detected through routine practice compared with those undergoing systematic annual screening. The results of the Pulmonary Hypertension and Recognition of Outcomes in Scleroderma (PHAROS) registry are also compelling, including a recent publication of the long-term outcomes of patients with SSc who were diagnosed with incident PAH by institutions that actively screen patients for PAH (31).

Humbert et al. (11) compared the outcomes between the patients enrolled in the French PAH Registry and the ItinérAIR-Sclérodermie program. They identified 16 patients whose PAH was diagnosed during scheduled echocardiographic assessment and 16 in whom PAH was diagnosed during routine clinical practice. The detection cohort had significantly higher survival rates of 8 years compared to the routine practice cohort, with 1-, 5-, and 8-year survival of 100%, 73% (95% confidence interval (CI) 43%-89%), and 64% (95% CI 33%-84%), respectively. The 8-year survival in the routine practice cohort was 17% (95% CI 3%-39%) in patients from the same treatment era. The hazard ratio for mortality risk in the routine practice cohort was 4.15 (95% CI 1.47-11.71) (11).

Patients whose PAH was diagnosed because of systematic screening also had better clinical measurements at diagnosis, with a higher proportion of patients meeting the New York Heart Association (NYHA) functional class criteria for class I and II. Patients diagnosed through screening also had better cardiopulmonary hemodynamics at RHC diagnosis of PAH, including lower right atrial pressure (RAP), lower mean pulmonary artery pressure (mPAP), and lower mean pulmonary vascular resistance index (PVR) (11).

These findings are consistent with similar improvements in the long-term outcomes reported in an Australian cohort of patients with SSc undergoing screening. Morrisroe et al. (9) reported the outcomes for patients enrolled in the Australian Scleroderma Cohort Study (ASCS) in which the patients are screened prospectively for the presence of cardiopulmonary complications using annual echocardiography, RFT, and 6-minute walk test (6MWT), if resources permitted. The group compared the outcomes of patients who were diagnosed with PAH at their first visit (who may have had prevalent PAH) with those of the patients who were diagnosed with incident PAH because of subsequent annual screening and found that 3-year survival was significantly better in the group diagnosed with PAH through subsequent screening. Furthermore, 3-year survival in the screened cohort from the time of PAH diagnosis was 94.7% compared to 42.7% ($p<0.001$) in the population diagnosed at the first visit (9).

Similarly, screening detected the patients with more favorable hemodynamic and prognostic characteristics at baseline, including significantly lower mean PVR, lower mPAP, and higher mean 6-minute walk distance (6MWD). Patients diagnosed with PAH on subsequent screens compared to the first screen were also more likely to be in a better World Health Organization functional class (9).

Results from the PHAROS registry also demonstrate that majority of the patients diagnosed with PAH because of the screening were classified as NYHA functional class I or II. Survival

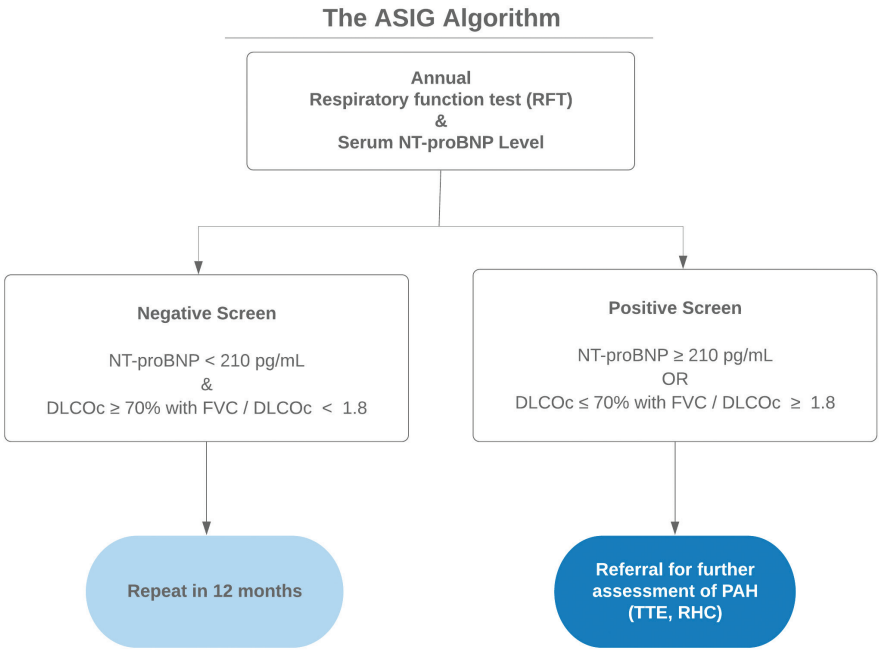

Figure 3. The Australian Scleroderma Interest Group (ASIG) algorithm.*
*The ASIG algorithm evaluates annual serum N-terminal probrain natriuretic peptide (NT-proBNP) level and FVC/DLCO ratio to determine the need for further assessment of pulmonary hypertension (PH) (21).
FVC: forced vital capacity % predicted; DLCO: diffusion capacity of the lung for carbon monoxide corrected % predicted; TTE: transthoracic echocardiography; RHC: right heart catheterization.

rates, when events were restricted to PAH-related deaths, at 1, 3, and 5 and 8 years after diagnosis were 97%, 83%, and 76%, respectively (31). The Ghent University SSc cohort also demonstrated lower mPAP at diagnosis of PAH after the implementation of screening in 2009 (32).

Cost savings

Available data suggest that screening programs for the systematic detection of PAH in patients with SSc can be cost saving. Analysis of the investigations performed during the ItinérAIR-Sclérodermie program revealed that 31 echocardiograms and 1.8 RHC were performed for each diagnosis of PAH with an estimated cost of £2,675 per diagnosis (11).

The average cost per patient attending the Ghent University Hospital SSc unit for PAH screening between February 2015 and February 2016 was estimated as EUR80 for annual echocardiography according to the 2009 ESC/ERS guidelines compared to EUR224 per patient screened using the DETECT algorithm. However, when patients underwent annual echocardiography according to the 2015 ESC/ERS guidelines in combination with the DETECT algorithm, the average cost of screening per patient was EUR112 (26).

Cost analysis of the ASIG algorithm (annual RFT and serum NT-proBNP) is performed by evaluating the cost of the ASIG algorithm compared to the screening with annual RFT and echocardiography. The NT-proBNP-based algorithm resulted in a cost saving of 14% per case of PAH diagnosed (19).

True cost-effectiveness analyses, incorporating the survival data and health-related quality of life data, are needed to definitively quantify the cost-effectiveness of the screening programs for SSc-PAH.

Research implications

Frequency of detection of "borderline PAH"

Following the 6th WSPH, an updated definition of precapillary PH was published. According to a scientific approach, precapillary PH is best defined by mPAP >20 mm Hg, pulmonary arterial wedge pressure ≤15 mm Hg, and PVR ≥3 Woods Units (33).

Vandecasteele et al. (26) addressed this in an analysis of 195 consecutive SSc patients screened using different algorithms. Borderline PH was defined as mPAP of 21-24 mm Hg during RHC. According to the DETECT algorithm, 13 of 14 patients (93%) with borderline PH were referred for diagnostic RHC, and according to the 2015 ESC/ERS guidelines, 10 of 14 patients with borderline PH (71%) were referred for RHC by screening with annual echocardiography (26).

Hoffmann-Vold et al. (34) likewise evaluated the incidence of borderline PH in an unselected cohort of 161 SSc patients attending the Oslo University Hospital before and after the implementation of the DETECT algorithm. Before the implementation of the DETECT algorithm, the patients were screened annually by complete clinical examination, echocardiogram, RFT, 6MWT, and NT-proBNP. They found no significant differences in the hemodynamic parameters at incident RHC between the cohort screened before the implementation of the DETECT algorithm and those screened by the DETECT algorithm. In the DETECT cohort, 26 patients (31%) were diagnosed with borderline PH compared with 13 patients (16.9%) in the cohort screened prior to the implementation of the DETECT algorithm (34).

A screening algorithm that incorporates risk stratification at baseline

Over the last 15 years, the therapeutic approach for the management of patients with PAH has evolved with the evidence for improved outcomes in the setting of selection of therapy based on multidimensional risk stratification of the severity of newly diagnosed PAH. Subsequent escalation of therapy, in a "treat-to-target" fashion, is based on the systematic evaluation of clinical response and maintenance or attainment of a low-risk status at follow-up. This in turn correlates with a much better long-term survival (35-37).

There exist several baseline and follow-up risk stratification calculators. The most frequently evaluated risk stratification tools are the Registry to Evaluate Early and Long-term PAH Disease Management risk score calculator and the risk table from the 2015 ESC/ERS PH guidelines (35).

Risk stratification is similar between the proposed calculators and includes the assessment of clinical characteristics, including the functional class, 6MWD, biochemical results, particularly NT-proBNP or BNP, and RHC hemodynamic parameters, such as RAP and mixed venous oxygen saturation (35). Therefore, a screening algorithm that incorporates the baseline evaluation of prognostic factors may contribute to a more streamlined evaluation and therapeutic strategy.

Conclusion

International registries of patients with SSc-PAH undergoing systematic screening for the

early detection of SSc-PAH have reported improvements in the survival with more patients being diagnosed in a low-risk status at the baseline. Best practice care of SSc should incorporate a screening program that facilitates a multidimensional PAH risk evaluation at the baseline and institution of early intervention with systematic clinical review of response to therapy guiding the therapeutic decisions.

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