



## REVIEW

# Screening for pulmonary arterial hypertension in systemic sclerosis

J-L. Vachiéry\* and G. Coghlan#

**ABSTRACT:** The onset and progression of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc) can be particularly aggressive; however, effective treatments are available. Therefore, early identification of patients with suspected PAH, confirmation of diagnosis, and intervention is essential. PAH may be challenging to diagnose in its earliest stages, particularly in populations that have multiple causes of breathlessness, and, therefore, screening is required. The optimal screening tools and methodology are, as yet, unknown, and this is confounded by a lack of consensus over which patients to screen. Current practice favours annual screening of all SSc patients using Doppler echocardiography to detect elevated right heart pressures. This will typically identify most patients with the various forms of pulmonary hypertension found in SSc. The optimum thresholds for Doppler echocardiography are still subject to investigation, especially for patients with mild pulmonary hypertension, and this technique may, therefore, yield a significant number of false-positives and a currently unknown number of false-negatives. Confirmatory right heart catheterisation remains necessary in all suspected cases. Further research is needed to identify the optimal tools and the screening approach with greatest specificity and selectivity.

**KEYWORDS:** Pulmonary arterial hypertension, screening, systemic sclerosis

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease (CTD) characterised by clinical heterogeneity and a high risk of complications and mortality [1]. SSc is associated with excessive inflammation, fibrosis and vasculopathy, the latter of which is a pivotal feature of several systemic manifestations of this disease. These include scleroderma renal crisis, pulmonary arterial hypertension (PAH) and digital ulceration.

The mortality associated with SSc has improved; however, it remains high [2–4]. Renal manifestations of SSc were historically the most lethal, but with the advent of more effective treatments, such as angiotensin-converting enzyme inhibitors for SSc renal crisis, there has been a change in the pattern of SSc-related mortality towards pulmonary manifestations [4]. PAH and interstitial lung disease are now the primary causes of late-stage disease morbidity and death among patients with SSc [4].

Patients with SSc may present various forms of pulmonary hypertension, as a consequence of chronic thromboembolism, interstitial lung disease or left heart disease. PAH is by far the most lethal form of pulmonary vascular disease and, like SSc,

is characterised by fibrosis, inflammation and vasculopathy. A large proportion of all patients who develop non-idiopathic forms of PAH do so in the context of a CTD. A French registry of 674 patients with PAH found that CTD-associated PAH accounted for 15.3% of the population, compared with 11.3% for congenital heart disease-associated PAH, and 39.2% for idiopathic PAH [5]. Similarly, data from 4,623 patients with PAH in 17 European countries observed that 22% (n=1,017) of the total population had PAH associated with SSc (PAH-SSc), and a further 5% (n=221) exhibited PAH associated with either systemic lupus erythematosus or mixed CTD [6].

The aim of this review is to examine the value of screening patients with SSc for PAH. There is a discussion of important considerations in selecting patients for screening, and the choice of screening tools. Finally, this review identifies gaps in our current knowledge and future directions for research.

## WHY IS SCREENING FOR PAH NECESSARY? *Morbidity and mortality of PAH*

PAH is a life-threatening disease that can rapidly progress to severe right heart failure [7, 8].

## AFFILIATIONS

\*Pulmonary Hypertension and Heart Failure Clinic, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.

#Royal Free and University College Medical School, London, UK.

## CORRESPONDENCE

J-L Vachiéry  
Pulmonary Hypertension and Heart Failure Clinic, Hôpital Erasme  
Université Libre de Bruxelles  
808 Route de Lennik  
1070 Brussels  
Belgium  
E-mail: jvachier@ulb.ac.be

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In addition, the condition carries a significant morbidity burden that includes impaired quality of life, frequent hospitalisations and rapidly evolving symptoms. The latter include dyspnoea and fatigue which are reflected by the New York Heart Association (NYHA) functional classification (table 1) [9, 10].

Survival of patients with PAH is poor. If untreated, the estimated median survival in idiopathic PAH is 2.8 yrs (95% CI 1.9–3.7; n=194) [11], and the prognosis is reported to be significantly poorer among patients with PAH-SSc [12]. An estimated 12% of patients with SSc develop PAH [13, 14], leading to a similar burden of disease as observed in other forms of PAH. Indeed, a recent observational cohort study of patients with isolated PAH-SSc in the UK reported a 3-yr survival of 47% [3].

### Effective treatments for PAH are available

A number of effective treatments are available for the management of PAH, including prostanoids, endothelin-receptor antagonists and phosphodiesterase type-5 inhibitors [15, 16]. A recent meta-analysis of 21 randomised controlled trials of a variety of these drugs in patients with various aetiologies of PAH (n=3,140) reported a reduction in all-cause mortality of 43% (relative risk (RR) 0.57, 95% CI 0.35–0.92; p=0.023) and reduction in hospitalisation of 61% (RR 0.39, 95% CI 0.25–0.61; p<0.001) [15]. Importantly, patients with PAH-CTD represented the second largest patient subpopulation after idiopathic PAH in these randomised trials.

In patients with SSc, improvements in exercise capacity and cardiopulmonary haemodynamics were observed in the only randomised, controlled trial undertaken exclusively in this population [17]. In an open-label study of bosentan in patients

with PAH associated with CTD (n=53, of whom 42 exhibited PAH-SSc), a survival rate of 92% at 48 weeks was observed [16]. The latter of these observations represents a significant achievement in this population, given the historically poor prognosis of these patients [3, 16]. In addition, subgroup analyses of pivotal studies with bosentan [18] and sitaxentan [19] support a substantial clinical benefit in this form of PAH.

These data demonstrate that therapeutic intervention in PAH-SSc can result in a successful outcome. In addition, recent data suggest that the simultaneous targeting of multiple pathogenic pathways using combinations of prostanoids, endothelin-receptor antagonists and phosphodiesterase type-5 inhibitors may also be beneficial [20–22].

### Early diagnosis and early intervention are essential

Early diagnosis of PAH-SSc and early subsequent intervention are essential for delaying disease progression [20]. However, diagnosis of PAH at the earliest stages of disease, *i.e.* NYHA functional class I and II, when patients have few or no symptoms, is challenging. Even when patients begin to deteriorate, early symptoms, such as breathlessness, fatigue and weakness, are nonspecific; therefore, patients may hesitate in presenting to their physician [23]. As a result, PAH-SSc is typically identified too late, with more than two-thirds of patients exhibiting symptoms in NYHA functional class III or IV at time of diagnosis (fig. 1) [3, 24, 25].

Early treatment is important. NYHA functional class at diagnosis has been observed to be predictive of mortality in both idiopathic PAH and PAH-SSc (fig. 2) [3, 7, 26]. Furthermore, in a recent study of patients with mildly symptomatic PAH (NYHA functional class II), a total of 14% of placebo-treated patients (n=92) experienced clinical worsening in 6 months [20], suggesting that treatment should be initiated at time of diagnosis.

These observations emphasise the need to seek early diagnosis and for early treatment of PAH in SSc patients [8, 20]. Because disease progression in patients with PAH-SSc can be rapid, delays in the diagnosis and treatment of PAH-SSc may reduce the likelihood of survival.

### Reasons for screening

In order to intervene early in the disease course, the prompt identification of SSc patients with undiagnosed PAH is necessary. In this specific population, screening plays a critical role and may also identify patients with other comorbidities, such as interstitial lung disease, which is an increasingly common burden in SSc, possibly as a result of improvements in patient survival in general. Notably, while treatment options for interstitial lung disease are limited, patients with interstitial lung disease and pulmonary hypertension are understood to exhibit a particularly poor prognosis [3].

In order to be of value, however, a screening strategy needs to possess an adequately predictive methodology to screen a targeted patient population.

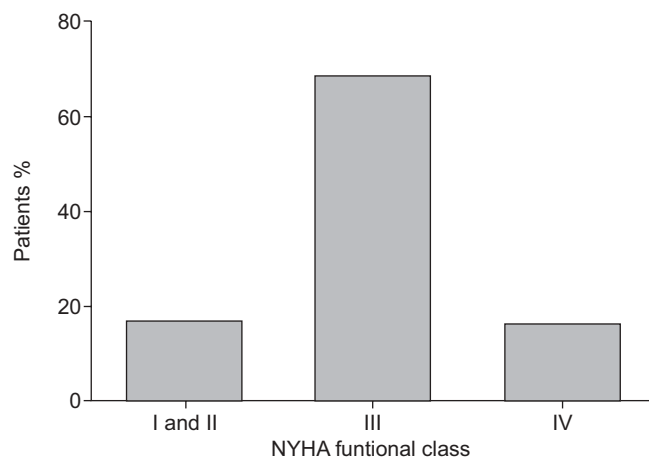
### PATIENT SELECTION FOR SCREENING

There are advantages and disadvantages to screening all patients with SSc for PAH *versus* only those who are symptomatic, *i.e.* those who present to a rheumatologist with

**TABLE 1** New York Heart Association classification of functional status

Class	Description
I	Patients with cardiac disease but without resulting limitation of physical activity Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain
II	Patients with cardiac disease resulting in slight limitation of physical activity Patients are comfortable at rest Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain
III	Patients with cardiac disease resulting in marked limitation of physical activity Patients are comfortable at rest Less than ordinary activity causes fatigue, palpitation, dyspnoea or anginal pain
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort Symptoms of heart failure or the anginal syndrome may be present even at rest If any physical activity is undertaken, discomfort is increased

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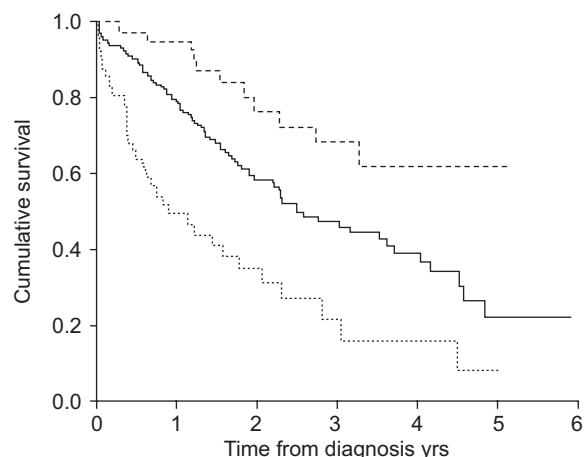
**FIGURE 1.** New York Heart Association (NYHA) functional class of patients with systemic sclerosis and incident isolated pulmonary arterial hypertension at time of diagnosis (n=259). Data taken from [3].

symptoms that prompt referral to a cardiologist or a pulmonologist.

Patients with SSc who are at the highest risk for PAH include those who first present with low diffusing capacity of the lung for carbon monoxide ( $DL_{CO}$ ; <50%) or who have declining  $DL_{CO}$  (e.g. >20% decrease over a 1-yr period), those with signs and symptoms, and those with prior echocardiographic abnormalities [14, 27–31]. A rheumatologist experienced in managing patients with SSc would undoubtedly refer such high-risk individuals to the relevant specialist. In addition, in many cases there will be a low threshold for suspicion among clinicians and patients that will hasten referral. However, this approach alone will fail to identify patients with nonspecific symptoms that may or may not be troublesome, such as those characteristic of early PAH. In addition, many patients can adapt to mild functional impairment, and this can be an issue of considerable concern with PAH. Furthermore, the prevalence of undiagnosed PAH in SSc may be important; one study estimated that 13.3% of patients with SSc or mixed CTD had increased pulmonary pressure during Doppler echocardiography that may correspond to undiagnosed pulmonary hypertension [32].

Clinicians may wish to screen patients with SSc for PAH only when symptoms are reported. In support of this practice, one may consider that trial-based improvements in 6-min walk distance may not be reflected in real life, that the available evidence is specific to patients with idiopathic PAH (and not PAH-SSc), that it is unfair to burden an asymptomatic patient with a diagnosis of a disease that cannot be effectively treated (such as interstitial lung disease), or that screening may not be cost-effective.

There are, however, robust arguments against the practice of screening only symptomatic patients in SSc. The evidence of efficacy in randomised controlled trials is reflected in clinically important end-points, such as mortality, hospitalisation and NYHA functional class [15], and has been, at least in part, extended specifically in the subgroup of patients with PAH-CTD [16, 18, 19, 33]. These data demonstrate that treatments for



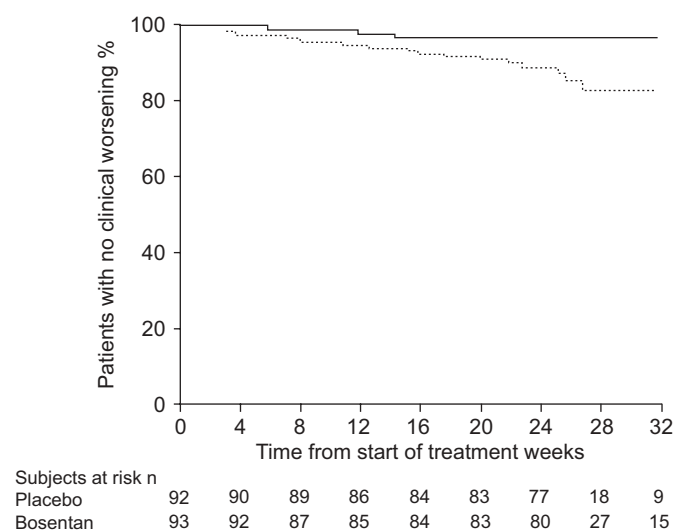
**FIGURE 2.** Survival from diagnosis of patients with isolated systemic sclerosis-associated pulmonary arterial hypertension grouped by New York Heart Association functional class (NYHA FC) ( $p < 0.001$ ). — — —: NYHA FC I/II; —: NYHA FC III; · · · · ·: NYHA FC IV. Reproduced from [3] with permission from the publisher.

**FIGURE 2.** Survival from diagnosis of patients with isolated systemic sclerosis-associated pulmonary arterial hypertension grouped by New York Heart Association functional class (NYHA FC) ( $p < 0.001$ ). — — —: NYHA FC I/II; —: NYHA FC III; · · · · ·: NYHA FC IV. Reproduced from [3] with permission from the publisher.

PAH are effective among the patient population that is likely to be identified by screening programmes. For example, the endothelin receptor antagonist bosentan has demonstrated efficacy in a patient subpopulation with PAH in NYHA functional class II (fig. 3) [20]. Furthermore, although patients in NYHA functional class II may be mildly symptomatic and have a well-preserved exercise capacity, some patients may be more severely affected haemodynamically; therefore, screening could offer an opportunity to identify such patients before they deteriorate further.

At present, no screening methodology can provide absolute certainty of diagnosis without confirmatory right heart catheterisation (RHC). Confirmation of diagnosis is important, as a patient with a malignant disease such as PAH may experience devastating consequences as a result of a false-negative diagnosis. One must, therefore, bear in mind that the frequency of screening is an important consideration. This may be seen to inconvenience patients without this aggressive manifestation; however, some patients among this high-risk group may instead appreciate the reassurance that screening provides.

Available data broadly support annual screening of all patients [24]. In a multicentre French study, patients with SSc and no severe pulmonary function abnormalities (n=570) were screened using Doppler echocardiography; those with a peak velocity of tricuspid regurgitation of  $>3 \text{ m}\cdot\text{s}^{-1}$ , or  $2.5\text{--}3 \text{ m}\cdot\text{s}^{-1}$  with unexplained dyspnoea, underwent RHC to confirm PAH [29]. At baseline, this screening process identified 18 patients who were subsequently newly diagnosed with PAH [29]. These newly diagnosed patients had PAH of mild severity, with mean pulmonary artery pressure ( $P_{pa}$ )  $30 \pm 9 \text{ mmHg}$  and mean total pulmonary resistance  $524 \pm 382 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$  [29], supporting the idea that screening may help identify patients at an early stage of disease. Prospective follow-up of the cohort



**FIGURE 3.** Time to clinical worsening in the EARLY (Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients) study of patients with pulmonary arterial hypertension in New York Heart Association functional class II, treated with bosentan (—) or placebo (· · · ·). Reproduced from [20] with permission from the publisher.

for 3 yrs, with regular repeat-screening, identified a further eight SSc patients who went on to develop PAH, at a mean of  $576 \pm 499$  days (median 408 days) from baseline [25]. Review of their original baseline data showed that five out of eight had been in NYHA functional class II or III, and five out of eight patients had exhibited  $DL_{CO} < 50\%$  predicted; and the absence of detectable tricuspid regurgitation at baseline did not exclude the risk of the occurrence of pulmonary hypertension within the following 3 yrs [25]. Due to the increased risk of mortality associated with PAH, annual screening is, therefore, justified [24].

The frequency of screening has obvious implications in terms of cost, resource use and patient convenience (and hence compliance). Even annual screening may be insufficiently frequent: while the asymptomatic period can be very long, patients may progress from asymptomatic to severely symptomatic in as little as 3–6 months. Frequent, repeated screening would likely identify incident cases earlier [25], although this would be associated with increased cost.

Available data also suggest that screening programmes can be cost-effective. In the French screening study [24, 25, 29], 31 echocardiograms and 1.8 catheterisations were performed for every confirmed diagnosis of pulmonary hypertension. Combining these rates with an estimated cost of £50 per echocardiogram and £625 per catheter, this gives an estimated cost of £2,675 per diagnosis. While this is a simplified example, and although repeat screening may also be necessary, other benefits such as the detection of interstitial lung disease, detection of impaired left heart function, reduced hospitalisation and improved quality of life, no doubt also contribute to cost-effectiveness of screening.

As discussed earlier, patients with other autoimmune and CTDs, such as systemic lupus erythematosus, are at risk of

developing pulmonary hypertension [32]. There may also be benefits of screening these patients for PAH, although at present, further data is required to support this.

## METHODOLOGY AND TOOLS FOR SCREENING

### Characteristics of a screening strategy

Critical factors that need consideration are the method and the strategy used, since a screening programme is only justified if the tools are efficient and reliable. An ideal screening tool or methodology would be easily available, noninvasive and inexpensive, producing reproducible results, with a high specificity and sensitivity.

As mentioned earlier, the only confirmatory test for PAH and, more broadly, pulmonary hypertension, is RHC [7]. RHC directly measures pulmonary pressures and can exclude post-capillary causes of pulmonary hypertension. The clinical utility of RHC as a screening tool is, however, limited by its invasive nature. Similar to other forms of the condition, the objective is to conduct confirmatory RHC only in patients with a high suspicion of PAH, and use less invasive screening tools to identify those patients requiring RHC.

### Initial evaluation: general assessment

In the setting of SSc, some tests are routine components of the clinical assessment and all help to raise suspicion of PAH. For example, a patient presenting with suspected PAH would broadly be expected to undergo evaluation of medical history, demographic characteristics, and characteristics of SSc, with categorisation of SSc subtype. Pulmonary function testing may also identify underlying lung disease and measures of exercise limitation (e.g. 6-min walk distance) and functional status (e.g. NYHA functional class) may also be helpful. These approaches alone are, however, unlikely to identify patients with asymptomatic PAH, and are nonspecific for patients in NYHA functional class I or II.

Chest radiography and ECG are also inadequate as screening tools. While chest radiographs may disclose abnormal anatomic features due to the presence of PAH, most patients with asymptomatic PAH exhibit normal findings [13]. ECG is considered to lack sufficient sensitivity to serve as a screening tool for PAH, and also has low specificity [13]. Other techniques, such as high-resolution computed tomography, require further research and are not considered to be diagnostic for the condition.

### Role of echocardiography in the screening strategy

Doppler echocardiography conducted at rest is considered to be the method of choice to screen for PAH, with different strategies employed to determine which patients require confirmatory RHC [7]. Echocardiography is useful because it can help in the differential diagnosis of pulmonary hypertension, identifying elevated pulmonary pressures due to systolic (and with variable accuracy, diastolic) left ventricular dysfunction. It can also detect right ventricular pressure overload or dysfunction and estimate  $P_{pa}$ ; calculations can derive the right ventricular systolic pressure, cardiac output and mean  $P_{pa}$  by pulmonary velocity. Several indices of right ventricular function, such as the tricuspid annulus plane systolic excursion and the right ventricular systolic performance index [7], can also be determined by this technique. In addition, Doppler echocardiography has also



TABLE 2

Correlation of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) and functional variables in pulmonary arterial hypertension associated with systemic sclerosis

Baseline NT-pro-BNP correlations	r	p-value
Mean pulmonary artery pressure	0.62	<0.0001
Pulmonary vascular resistance	0.81	<0.0001
Right atrial pressure	0.53	<0.0001
Cardiac index	-0.5	<0.0001
Mixed venous oxygen saturation <sup>#</sup>	-0.46	0.013
6-min walk distance	-0.46	<0.0001

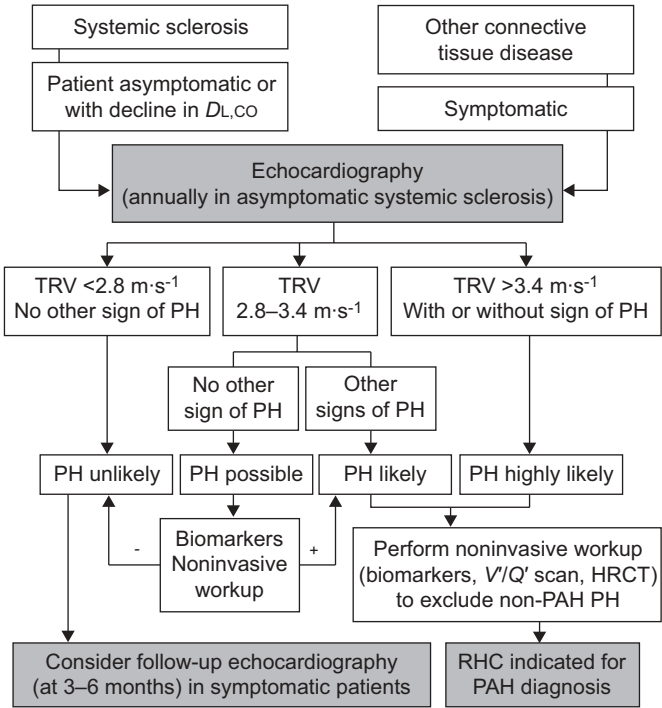
<sup>#</sup>: data taken from [50]. Reproduced from [49] with permission from the publisher.

proven to be sensitive to interventions [34]. This versatility increases its utility as a screening tool.

The most common method to detect pulmonary hypertension by echocardiography is based on the estimate of the right ventricular systolic pressure by means of the maximal tricuspid regurgitation velocity (TRV) [7]. A confirmatory RHC is recommended for patients with TRV >3.4 m·s<sup>-1</sup> (corresponding to a systolic P<sub>pa</sub> >50 mmHg) or in patients with a TRV between 2.9 and 3.4 m·s<sup>-1</sup> (corresponding to a systolic P<sub>pa</sub> between 34 and 49 mmHg) in the presence of other signs suggestive of pulmonary hypertension [35]. Based on the estimation of the systolic P<sub>pa</sub>, echocardiography has an approximate sensitivity of 0.79–1.00 for the detection of pulmonary hypertension, with a specificity of 0.6–0.98 [10].

Despite these merits, echocardiography is not diagnostic for PAH and presents important limitations. Although this technique may accurately detect PAH at an early stage, it cannot accurately discriminate between underlying causes of pulmonary hypertension [24, 25, 29]. Another important issue is that the true definition of pulmonary hypertension is based on mean P<sub>pa</sub> measured by RHC, whereas echocardiography estimates systolic P<sub>pa</sub>. In addition, echocardiography is also associated with a high rate of false-positive identification [36]. Finally, there is no clear definition of normal range for echocardiographic estimates of systolic P<sub>pa</sub> that increases with age and body mass index [37]. Therefore, the sensitivity, specificity and predictive value of echocardiography in the setting of PAH depend on the thresholds used for normal values [38]. Screening algorithms for SSc patients have been developed and revised in order to improve the diagnostic accuracy of echocardiography [25, 29]. Notably, the threshold used to prompt RHC in the French ItinérAIR study was set for a TRV at 3.0 m·s<sup>-1</sup> or between 2.5 and 3.0 m·s<sup>-1</sup> in the presence of unexplained dyspnoea [29].

Research into further iterative improvements in echocardiography is underway. For example, Doppler echocardiography conducted during stress/exercise may be useful [39–41]. This method may detect an abnormal response of the pulmonary circulation under a defined stress, and reflects physiological changes seen with daily activity. The use of a specific setting has improved standardisation in terms of measurement and



**FIGURE 4.** Proposed screening algorithm for identification of pulmonary arterial hypertension (PAH) associated with connective tissue disease. Echocardiography should be performed as a screening tool for pulmonary hypertension (PH) in asymptomatic patients with systemic sclerosis and/or in patients with other connective tissue disease with suspected symptoms. Right heart catheterisation (RHC) is indicated in patients for whom PH is likely or highly likely. Repeated echocardiography should be considered if the initial exam was inconclusive or in cases of symptomatic progression. DL<sub>CO</sub>: diffusing capacity of the lung for carbon monoxide; TRV: tricuspid regurgitation velocity; V/Q: ventilation/perfusion; HRCT: high-resolution computed tomography.

loading conditions. At present, data are conflicting as to whether or not exercise echocardiography can detect asymptomatic pulmonary hypertension in patients with SSc, and further research is necessary [42–45].

**Biomarkers**

Other tools currently have less evidence associated with them, including biological markers such as N-terminal pro-brain natriuretic peptide (NT-pro-BNP), uric acid, troponin and norepinephrin [46–52]. NT-pro-BNP correlates with survival in primary pulmonary hypertension [47], and with NYHA functional class, exercise capacity and cardiopulmonary haemodynamics in PAH-SSc (table 2) [49, 50].

In a study of 40 patients with SSc [53], 13 patients had high NT-pro-BNP values for their ages. Such high NT-pro-BNP levels identified patients with PAH with a sensitivity of 90%. A specificity of 90.3% was also observed, with a positive predictive value of 69.2%, and a negative predictive value of 96%.

A number of autoantibodies specific to SSc have also been observed to be associated with, albeit not specific to, PAH. These include anti-centromere [54], anti-U1 ribonucleoprotein [55], anti-U3 ribonucleoprotein [56], anti-Th/To [57] and anti-phosphoprotein B23 [58] antibodies. Their apparent lack of

**TABLE 3** Visit and assessment schedule in the DETECT study

	Cross-sectional stage		Longitudinal change		
	Screening	Baseline	Year 1	Year 2	Year 3 or earlier <sup>#</sup>
Informed consent <sup>†</sup>	Yes				
Check of eligibility criteria	Yes				
Demographics	Yes				
Medical history	Yes				
Pulmonary function tests <sup>+</sup>	Yes		Yes	Yes	Yes
Concomitant medication		Yes	Yes	Yes	Yes
SSc characteristics		Yes	Yes	Yes	Yes
Serum analysis by central lab		Yes			Yes
Serum storage by central lab		Yes	Yes	Yes	Yes
Physical examination		Yes	Yes	Yes	Yes
Echocardiography		Yes	Yes	Yes	Yes
ECG		Yes	Yes	Yes	Yes
RHC <sup>§</sup>		Yes			Yes
6MWT, Borg dyspnoea index		Yes	Yes	Yes	Yes
NYHA functional class <sup>‡</sup>		Yes			Yes

SSc: systemic sclerosis; RHC: right heart catheterisation; 6MWT: 6-min walk test; NYHA: New York Heart Association. <sup>#</sup>: earlier in case of suspected pulmonary hypertension before year 3 requiring RHC, or for patients predictably unable to stay in the study; <sup>†</sup>: obtained before any invasive procedure; <sup>+</sup>: diffusing capacity of the lung for carbon monoxide/alveolar volume, forced vital capacity, forced expiratory volume in 1 s, total lung capacity and residual volume; <sup>§</sup>: RHC performed as last test in order to exclude bias regarding any other test but not later than 2 months after the other tests; pregnancy is contraindicated; <sup>‡</sup>: for patients diagnosed with pulmonary arterial hypertension or pulmonary hypertension.

specificity is typical of biomarkers for PAH-SSc, and further elucidation of their role in screening for PAH is needed.

At present, little is known about the value of these tools when used in combination. The correlation between NT-pro-BNP with other tools would appear to suggest that such an approach would have enhanced diagnostic capabilities; however, this is not known and further research is needed to confirm the discriminatory value in such an approach.

### Importance of an integrated approach

Effective screening programmes need not use only sophisticated diagnostic tools. Patient education is beneficial, and patients should be encouraged to report symptoms following a decline in clinical status. In turn, physicians should be encouraged to repeat screening tests in cases where there is clinical suspicion of cardiac or pulmonary involvement. There may also be value in a nurse specialist speaking with patients by telephone at regular intervals, to investigate if patients have deteriorated. While these approaches have some obvious limitations, *e.g.* asymptomatic patients will not be identified using these methods alone, these approaches may add value within a screening programme.

### FUTURE OF SCREENING

In the absence of robust, prospective data to support an optimal screening strategy for PAH in SSc, guidelines on the general management of PAH, developed by a joint committee of the European Respiratory Society and European Society of Cardiology, will provide general guidance [7, 33]. Based largely on echocardiography findings, these guidelines provide

consensus for informing clinical practice as well as designing clinical trials. Figure 4 shows a proposed algorithm that is based on these guidelines and uses an integrated approach to screening.

The ongoing DETECT (early, simple and reliable detection of PAH in SSc) study will address the need for robust prospective data pertaining to the optimal identification of undiagnosed PAH in patients with SSc. The objective of DETECT is to improve the management of PAH and pulmonary hypertension in SSc by identifying simpler and more reliable screening tools to facilitate early detection. It is an international, multicentre, prospective, observational cohort study in two stages: the first stage is cross-sectional and will evaluate various methods for screening PAH *versus* RHC; the second stage is a longitudinal 3-yr follow-up to evaluate the incidence of PAH and to identify potential prognostic factors for PAH. Screening tests that will be evaluated in the estimated 500 patients recruited include 6-min walk distance, Borg dyspnoea index, a range of echocardiographic parameters, ECG, potential biomarkers, pulmonary function tests, medical history, demographics and SSc characteristics (table 3).

The results of the DETECT study will assist in the identification of single or multiple screening tests for early detection of PAH in SSc patients, and are expected to influence future PAH and pulmonary hypertension screening guidelines and management of SSc patients. If identified, a convenient noninvasive tool or methodology for PAH and pulmonary hypertension in SSc patients would be expected to impact standards of care in a variety of clinical settings beyond SSc.

## CONCLUSIONS

In conclusion, PAH is an aggressive and malignant manifestation of vasculopathy in SSc that causes considerable morbidity and mortality, and necessitates early diagnosis and intervention. Efficacious therapeutic interventions for PAH are available and can be used alone or in combination to mitigate disease progression. Given that patients with SSc are at significantly increased risk of developing PAH compared with the general population, they should be screened using echocardiography at least annually. Several other screening tools are available, although further supportive data are needed for many. The ongoing DETECT study will provide robust prospective data that quantifies the value of many potential screening tools, enabling more reliable strategies for screening PAH to be employed in the future.

## STATEMENT OF INTEREST

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