Published in final edited form as:
Arthritis Rheum. 2013 December ; 65(12): . doi:10.1002/art.38172.

Recommendations for Screening and Detection of Connective-Tissue Disease Associated Pulmonary Arterial Hypertension

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Abstract

Objectives—Pulmonary arterial hypertension (PAH) affects up to 15% of patients with connective tissue diseases (CTD). Previous recommendations developed as part of larger efforts in PAH did not provide detailed recommendations for patients with CTD-PAH. Therefore, we sought to develop recommendations for screening and early detection of CTD-PAH.

Methods—We performed a systematic review for the screening and diagnosis of PAH in CTD by searching the literature. Using the RAND/UCLA methodology, we developed case scenarios followed by 2 stages of voting—first international experts from a variety of specialties voted anonymously on the appropriateness of each case scenario and then the experts met in a face-to-face meeting to discuss and resolve discrepant votes to arrive at consensus recommendations.

Results—The key recommendations state that patients with systemic sclerosis (SSc) should be screened for PAH. In addition, mixed connective tissue diseases (MCTD) or other CTD's with scleroderma features should also be screened for PAH (scleroderma-spectrum disorder). Initial screening evaluation in patients with SSc and scleroderma-spectrum disorders include pulmonary function test (PFT) including diffusion capacity carbon monoxide (DLCO), transthoracic echocardiogram (TTE), and NT- Pro BNP. In SSc and spectrum disorders, TTE and PFT should be performed on annual basis. The full screening panel (TTE, PFT, and NT-ProBNP) should be performed as soon as any new signs or symptoms are present.

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Management of Conflict: These recommendations focus on screening and early detection of connective tissue disease-associated pulmonary arterial hypertension. Management (including treatment) is not addressed by these recommendations.

Conclusion—We provide consensus-based, evidence-driven recommendations for screening and early detection of CTD-PAH. It is our hope that these recommendations will lead to earlier detection of CTD-PAH and ultimately improve patient outcomes.

Keywords

Pulmonary hypertension; pulmonary arterial hypertension; connective tissue diseases; systemic sclerosis; recommendations; guidelines

INTRODUCTION

Pulmonary arterial hypertension (PAH) affects 0.5–15% of patients with connective tissue diseases (CTD) and is one of the leading causes of mortality in systemic sclerosis (SSc) and mixed connective tissue disease (MCTD) (1–5). Despite increasing recognition of PAH in CTDs, the diagnosis is often delayed, which may lead to unfavorable outcomes in these patients (2, 6). International organizations have provided recommendations for screening and detection of PAH in CTDs, but these recommendations have been limited to the utilization of transthoracic echocardiography for patients with SSc (7–9). The established recommendations were developed as part of larger efforts in PAH and did not provide detailed recommendations for patients with other CTD-PAH. Therefore, we sought to develop recommendations for screening and early detection of CTD-PAH using rigorous data-driven and consensus-building methodology that has been used previously to develop recommendations.

These recommendations are designed to promote screening and early detection of CTD-PAH, and to reflect best practice, as evaluated by a diverse group of experts who examined the current level of evidence. Important design limitations of the RAND/UCLA Appropriateness Methodology that was used in this study are the lack of inclusion of societal costs of health care, nor the cost and cost-effectiveness of tests in the analyses (10). These recommendations are not meant to be prescriptive and are based on currently available evidence. The recommendations cannot and should not substitute for individualized direct assessment of the patient, coupled with clinical decision making by a competent health care practitioner. Importantly, the recommendations presented here are not intended to limit or deny third party payer coverage of health care costs for groups, or individual patients.

METHODS

Project design and development of recommendations and grading of evidence

The RAND/UCLA consensus methodology, developed in the 1980s, incorporates both Delphi and nominal group methods, and was successfully used to develop other guidelines and recommendations commissioned by the American College of Rheumatology (11–14). The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical decision-making. The RAND/UCLA method requires 2 groups of experts—a core expert panel (CEP) that provides input into case scenario development and preparation of a scientific evidence report, and a task force panel (TFP) that votes on these case scenarios. A systematic review of pertinent literature was performed that focused on PAH(15) and excluded articles that assessed World Health Organization (WHO) groups 2 and 3 (detailed in Appendix 1), and the resultant scientific evidence report was given to the TFP in conjunction with clinical scenarios representing a broad scope of disease. The scenarios illustrated multiple questions of interest and alternative options.

The CEP consisted of 2 experts in CTD-PAH (1 rheumatologist and 1 cardiologist), 2 trainees in rheumatology who conducted the systematic review, and 1 expert in RAND/UCLA. The TFP consisted of diverse group of experts—3 rheumatologists, 1 internist, 4 pulmonologists, and 2 cardiologists, all with extensive experience and publications in the field of pulmonary vascular disease. There were 2 rounds of ratings. First, members of the TFP anonymously ranked each of the potential elements of the recommendations on a risk-benefit basis ranging from 1 to 9 on a Likert scale using Delphi process. A vote of 1–3 was weighed as ***Inappropriate***= risks clearly outweigh the benefits. A vote of 4–6 was considered ***Uncertain***= risks-benefit ratio is uncertain. A vote of 7–9 was weighed as ***Appropriate***= benefits clearly outweigh the risks. Votes on case scenarios were translated into recommendations if the median voting score was between 7–9 ("appropriate") and if there was no significant disagreement, defined as no more than 1/3 of the votes between 1–3 ("inappropriate") for the scenario. For the second round of voting, the TFP and CEP convened for a face-to-face meeting to review results of first round voting. All TFP members attended the meeting. During this meeting, a moderator experienced in the RAND/UCLA methodology (JF) led a discussion of the first round voting results. Where areas of discrepancy were identified, discussion between members of the TFP (and CEP when requested by the TFP) was used to clarify discrepant viewpoints and reach consensus where possible.

A priori, the votes on scenarios resulting as "appropriate" (median vote 7–9, without significant disagreement – defined by 1/3 or more votes in the 1–3 range) were included as recommendations. "Inappropriate" results (median vote 1–3) were not included as negative recommendations. During the face-to-face TFP meeting, some case scenarios were clarified for content based on TFP discussion and re-voted on by the TFP as necessary.

To evaluate the risk of bias and quality of our studies we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) evaluation tool (16, 17). QUADAS assesses the risk of bias in 4 domains including patient selection, index test, reference standard, and flow and timing. Studies receiving low risk in all domains have the highest quality. Based on the results from the QUADAS evaluation, we also assigned the quality of evidence as proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (18, 19). Briefly, a recommendation is assigned as **High quality** if further research is unlikely to change the recommendations, **Moderate quality** if further research is likely to affect our recommendations and may result in change, **Low quality** if further research is very likely to affect our recommendations and likely result in change, and **Very low quality** if recommendations are uncertain. GRADE quality rating reflects the published evidence available to support a recommendation.

Definitions for the case scenarios

For these recommendations, **screening** is defined as "the presumptive identification of unrecognized disease by the application of tests, examinations, or other procedures which can be applied rapidly."(20) This assumes that a patient has no symptoms attributable to pulmonary hypertension (PH). **Detection** is defined as the identification of patients with signs and/or symptoms attributable to PH. The definition of a particular CTD was based on the published criteria by rheumatology associations such as American College of Rheumatology (21) or different authors (22–25). However, the panel acknowledged that diagnosis of a CTD is based on physician's evaluation of the patient, as classification and diagnostic criteria are not synonymous. In addition, it was agreed that a patient could have more than one CTD if they met the published criteria. A glossary is provided for the terminology used in these recommendations as Appendix 2.

RESULTS

General recommendations (Table 1)

The TFP voted that every patient with SSc should be screened for PAH due to the high prevalence of PAH in SSc (Moderate quality evidence [**QE**]) (1, 2, 26). In addition, MCTD or other CTD's with prominent scleroderma features (such as sclerodactyly, nail fold capillary abnormalities, or scleroderma-specific autoantibodies), referred to hereon as scleroderma-spectrum disorders, should also be screened for PAH due to high risk of PAH in these patients (Very low QE) (8, 27). Screening was not recommended for MCTD or CTD patients without features of scleroderma as the prevalence of PAH is either low or poorly defined in these patient populations (Low to moderate QE) (4, 8, 28). RHC was voted as mandatory for diagnosis of PAH in all patients (High QE). It was emphasized that PAH be defined by a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg with a pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg (28) on resting RHC. Additional diagnostic criteria may include a pulmonary vascular resistance of >3 Wood units (7) in the presence of either normal or reduced cardiac output. In all cases, chronic thrombo-embolic-PH (WHO Group 4) must be excluded by either ventilation/perfusion lung scanning, helical computer tomography or conventional pulmonary angiogram (7). Ventilation/perfusion lung scanning is the preferred diagnostic test (29) but may be suboptimal with concomitant lung fibrosis.

Patients with SSc and scleroderma-spectrum disorders with a positive non-invasive screen (as presented in the next section) should be referred for RHC (High QE).

Initial evaluation in patients with SSc and scleroderma-spectrum disorders

It was recommended that screening pulmonary function tests (PFT; spirometry with lung volumes) with single breath diffusion carbon monoxide (DLCO) (High QE), transthoracic echocardiogram (TTE) (High QE), and N-terminal pro-B-type natriuretic peptide (NT-Pro BNP) (Moderate QE) in all patients with SSc and scleroderma-spectrum disorders. The panel also endorsed the DETECT (DETECTion of PAH in SSc) algorithm in these patients if their DLCO < 60% and > 3 years of SSc disease duration from the time of the first non-Raynaud's symptom (Moderate QE)(30).

Frequency of non-invasive tests

The TFP recommended that TTE and PFT should be performed on an annual basis on all SSc (Low QE) and SSc-spectrum patients (Very low QE). At the onset of any new signs or symptoms of pulmonary hypertension, TTE (High QE), PFTs (Low QE) and NT-Pro-BNP (Low QE) should be performed.

Referral for right heart catheterization (Table 2)

The TFP recommended that acute vasodilator testing during RHC is not required as part of the evaluation of PAH as the proportion of patients with a positive vasodilator test (defined as reduction in mean PAP by at least 10 mmHg to a mean PAP of less than 40 mmHg in the setting of a normal cardiac output) and long-term response to calcium channel blockers in this population are negligible (Moderate to high QE) (8, 31). However, though not voted, it was discussed that there may be other reasons that individual physicians may wish to perform vasodilator challenge in these patients (e.g. insurance requirements).

In patients with SSc and scleroderma-spectrum disorders and signs and/or symptoms of PH, the TFP voted that a TR jet of 2.5–2.8 m/sec (equating to a trans-tricuspid gradient of 25 mmHg to 32 mmHg) should be referred for RHC (High QE). In addition, all patients (with or without signs and/or symptoms of PH) with TR jet > 2.8 m/sec (equating to a trans-tricuspid gradient of >32 mmHg) should be referred for RHC (High QE). Moreover, for all

patients with right atrial or right ventricular enlargement (RA major dimension >53 mm and RV mid cavity dimension > 35 mm), irrespective of TR jet (including non-measurable or < 2.5 m/sec) should be referred for RHC (High QE). A RHC was recommended for patients with signs or symptoms of PH and an FVC%/DLCO% ratio > 1.6 and/or a DLCO <60% where a TTE did not reveal overt systolic dysfunction, greater than grade I diastolic dysfunction, greater than mild mitral or aortic valve disease or evidence of PH (as defined above) (High QE). Other scenarios are discussed in the Table 2. In MCTD or other CTD's without scleroderma features, the presence of unexplained signs and symptoms of PH should lead to consideration of the published diagnostic algorithm for PH (Low QE).

Scenarios were discussed regarding the need for serial screening in CTD patients with normal RHC who might subsequently meet the above recommended indications for RHC during follow-up visits, but could not reach firm recommendations due to lack of published data. However, the panelists emphasized the need for clinical judgment on a patient-by-patient basis, and further research in this area. The panelists did not provide recommendations on borderline mPAP (21–24mmHg) or exercise PH due to lack of long-term outcomes data and variability in exercise testing (32, 33). The panelists did agree that this is an important research agenda for patients in 'high-risk' group such as SSc and scleroderma-spectrum disorders. In addition, there was no consensus on the definition of moderate-to-severe ILD to classify a patient in the WHO group 3. The panelists felt that further research is needed to define this and current published definitions should be used for these recommendations.

DISCUSSION

We present the first evidence- and consensus-based recommendations for screening and early detection of CTD-associated PAH. The recommendations are written for health care providers who evaluate and treat patients with CTDs (such as rheumatologists and primary care physicians). The recommendations are presented to encourage screening and, therefore, early diagnosis of CTD-associated PAH. Screening is defined as the systematic testing of asymptomatic individuals for preclinical disease(20). The purpose of screening and early detection is to identify those with asymptomatic / preclinical disease and mildly symptomatic patients in order to prevent or delay progression of disease through early management. Screening programs play an important part in the detection of PAH in certain "at-risk" populations and may enable patients to be identified at an earlier stage than in routine clinical practice. This is particularly important in patients with CTD's who may be relatively sedentary, and therefore may not develop symptoms until their disease is quite advanced. However, screening tests are not meant to be diagnostic and appropriate tests (RHC in case of PAH) should be performed to make a diagnosis.

Prevalence of PAH is 8–12% in patients with SSc and is responsible for almost 30% of SSc-related deaths (34). In a single center study of patients with MCTD, 64% of mortality was attributed to PAH at mean follow up of 15 years(3). Other CTDs have also shown to be associated with PAH(4, 5, 35). The value of screening for PAH in patients with SSc has been highlighted by the recent work of Humbert and colleagues (2). In this prospective study, SSc patients whose PAH was detected in an early detection program (n=16) were compared with SSc patients whose PAH was diagnosed during routine clinical practice (n=16). At the time of PAH diagnosis detected patients had less advanced pulmonary vascular disease than patients identified in routine daily practice (36). At diagnosis, 6% of patients detected by screening were in New York Heart Association Functional Class (NYHA FC) I and 44% were in NYHA FC II. These results contrast sharply with those from the patients diagnosed in routine practice, in which the majority of patients were already in NYHA FC III or IV at the time of diagnosis (69% and 18.5%, respectively). Patients in the

screening program had significantly higher survival at 8 years than patients identified by routine daily practice (64% versus 17%; p=0.004). The small sample size and effect of lead-time bias may have led to this effect and needs to be confirmed in a larger study.

The resultant recommendations from the TFP take into account recommendations from professional societies, as well as systematic review of the published studies (15). The European Society of Cardiology (ESC)/European Respiratory Society (ERS) (8), which recommends annual TTE screening in symptomatic SSc patients, and annual screening in asymptomatic SSc patients 'may be considered' (7). Similar to our recommendations, the American College of Cardiology Foundation/ American Heart Association recommend yearly TTE and referral for RHC if TTE argues for elevated pulmonary artery pressure (high right ventricular systolic pressure estimates or enlargement of right heart chambers) (7). The American College of Chest Physicians recommends TTE for clinical suspicion for PAH in order to evaluate for elevated estimated RVSP and right atrial and ventricular enlargement (9).

However, none of the published recommendations include use of other non-invasive screening tests, such as PFTs, and serum biomarkers (NT-proBNP), that have been shown to be associated with PAH in SSc patients(30, 37–40). For example, the ItinérAIR-Sclérodermie PAH detection study screened 195 patients with symptoms consistent with PAH with SSc. Gas transfer analyses determined that DLCO was ≤60% in 162 patients, of whom 13 (8%) had PAH (41). Also, in a recent prospective cohort, the presence of an elevated NT-Pro BNP (>97th percentile of normal) and a DLCO/VA % predicted of < 70% was associated with a hazard ratio of 47.2 for developing PAH at 36 months (39). Finally, NT-Pro BNP was found to be a good screening test in 2 large cohorts with SSc (38, 40).

A combination of TTE and PFT might be used to enrich the screening population with SSc (30, 39, 42, 43); a recent study proposed a representative algorithm of non-invasive tests to screen/ early detection of SSc-PAH (30). In the DETECT study that included patients with SSc and scleroderma-spectrum disorders, an enriched cohort of 466 patients (adult patients of >3 years' duration from first non-Raynaud's symptom and a predicted DLCO of <60%) underwent non-invasive testing and RHC. Of these, 87 (19%) had RHC-confirmed PAH(30). However, DETECT study does not provide recommendations regarding patients with DLCO≥ 60% or patients where DETECT screening is negative and needs to be validated in another cohort.

The TFP recommended referring patients with TR jet of 2.5–2.8 m/sec with signs or symptoms of PAH to RHC and referring patients with TR jet > 2.8 m/sec, irrespective of signs or symptoms of PAH, to RHC. This is supported by large cohort studies where a TR jet of >2.73 to 3.0 m/sec without signs or symptoms of PAH or >2.5 m/sec with symptoms were used for referral for RHC (41, 44–47). The right ventricular systolic pressure on TTE can be estimated by the modified Bernoulli equation, $4(TRV)^2$ + right atrial pressure (RAP). Guidelines for the estimation of RAP based on inferior vena cava diameter and respiratory variation have been established, but are most accurate at the extremes (48). However, in reality, there is variation in how echocardiographers add the estimated RAP from one echo laboratory to another and even amongst echocardiographers in the same laboratory. Tricuspid regurgitant velocities (TRV) of 2.5 m/s, 2.8 m/s, and 3.0 m/s correspond to trans tricuspid velocities of 25 mmHg, 31 mmHg, and 36 mmHg respectively. Thus, the variation of 5–10 mmHg for the estimated RAP has the potential to alter the decision making process for an individual patient. To reduce this variability, we chose to base criteria on TRV rather than estimated RVSP. This approach, while methodologically sound, may not be applicable in broad clinical practice as many echocardiography laboratories report out estimated RVSP

as opposed to TRV. For practical purposes, a TRV of 2.5 m/s corresponds to an estimated RVSP of 30–35 mmHg assuming a RAP of 5–10 mmHg.

The TFP recommended performing non-invasive TTE and PFT on an annual basis in patients with SSc and scleroderma-spectrum disorders. Although there is lack of evidence regarding the frequency of tests, high incidence of PAH is observed in these patients. In addition, an annual TTE is consistent with some of the other recommendations in SSc (7, 8). The societal economic costs of such recommendations are unclear. Early treatment may improve outcomes (acknowledging that knowledge gaps still exist in SSc-PAH). This could lower medical costs to care for patients with milder disease. However, it could theoretically increase medical costs to society through expensive medical therapies for PAH or through extended courses of care (through greater longevity). The costs of screening and the potential impact of those results are complicated and beyond the scope of this project. The RAND/UCLA excludes cost-efficacy considerations as this would require separate literature dataset for decision making. Further research is needed in this area.

Our study has many strengths. We used an established consensus methodology(49) that has a foundation in rheumatology and been used in recent guidelines supported by the American College of Rheumatology(11–13, 50). In addition, we assessed the quality of the studies using the QUADAS evaluation. A majority (16/22) of our studies were cohort studies and were rated as high quality of evidence (low risk of bias or applicability concerns) on the QUADAS evaluation scale(15). We followed the GRADE methodology to assign quality to the recommendations. The majority of the recommendations are of moderate-to-high quality. Also, we had a diverse group of experts (cardiologists, internist, pulmonologists, rheumatologists) who participated as the panelists.

Limitations of the recommendations include the RAND/UCLA methodology utilized for this project as it did not allow us to address the important societal implications of screening or early detection of PAH. For example, the costs of proposed screening tests are not considered in these recommendations. This assumption is not different than other recommendations published in medicine using this methodology. Also, the treatment was not evaluated as part of these recommendations.

In conclusion, we provide consensus-based and evidence-driven recommendations for screening and early detection of CTD-PAH. It is our hope that these recommendations will lead to early detection of CTD-PAH and ultimately improve patient outcomes. As with any recommendations, these should be updated as more evidence becomes available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Mr. Robert Riggs from the Scleroderma Foundation and Mr. Rino Aldrighetti from the Pulmonary Hypertension Association.

FUNDING

The project was funded by the Scleroderma Foundation and Pulmonary Hypertension Association. The Scleroderma Foundation and Pulmonary Hypertension Association received unresticted educational grants from Actelion, Gilead, and United Therapeutics to support development of these recommendations. Dr. Khanna was also supported by NIH/NIAMS K24 AR063120–02. Dr. Chung receives funding from the Scleroderma Research Foundation. Dr. Mathai receives funding from the NHLBI/PHA jointly sponsored K23 HL093387.

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Table 1

General recommendations for screening and early detection of CTD-PAH. GRADE quality of evidence is present in parenthesis next to each statement

- All patients with systemic sclerosis (SSc) should be screened for PAH. **(Moderate quality)**
- MCTD or other CTD's with scleroderma features (referred hereon as scleroderma-spectrum disorders) should be screened similar to patients with SSc. **(Very low quality)**
- Screening of asymptomatic patients is not recommended for MCTD or other CTD (including systemic lupus erythematosus, rheumatoid arthritis, inflammatory myositis, Sjögren's syndrome) patients **without** features of scleroderma. **(Low to Moderate quality)**
- For unexplained signs and symptoms of PH in patients with MCTD, SLE or other CTD's without scleroderma features, one may consider the diagnostic algorithm work-up for PH. **(Moderate quality)**
- All SSc and scleroderma-spectrum patients with a positive non-invasive screen (as presented in these recommendations) should be referred for right heart catheterization (RHC). **(High quality)**
- RHC is mandatory for diagnosis of PAH. **(High quality)**
- Acute vasodilator testing is not required as part of the evaluation of PAH in patients with SSc, SSc-spectrum disorders, or other CTD. **(Moderate to High quality)**

Initial screening evaluation in patients with SSc and scleroderma-spectrum disorders

- PFT with diffusion capacity carbon monoxide (DLCO) **(High quality)**
- Transthoracic echocardiogram (TTE) **(High quality)**
- NT- Pro BNP **(Moderate quality)**
- DETECT algorithm if DLCO% < 60% and >3 years disease duration **(Moderate quality)**

Frequency of non-invasive tests

- TTE on annual basis as a screening test **(Low quality)**
- TTE if new signs or symptoms develop **(High quality)**
- PFT with DLCO on annual basis as a screening test **(Low quality)**
- PFT with DLCO if new signs or symptoms develop **(Low quality)**
- NT-Pro BNP if new signs of symptoms develop **(Low quality)**

Table 2

Recommendations for right heart catheterization for SSc and scleroderma-spectrum disorder

		Signs or symptoms* required for RHC	Quality of Evidence
TTE	TR velocity		
	• 2.5–2.8 m/s	Yes	High
	• > 2.8 m/s	No	High
	Right atrial (RA major dimension >53 mm) or right ventricular enlargement (Mid cavity RV dimension > 35 mm), irrespective of TR velocity	No	High
PFTs	FVC/DLCO ratio > 1.6 and/or DLCO <60%**	Yes	High
	FVC/DLCO ratio >1.6 and/or DLCO<60% and NT-Pro BNP >2 times upper limit of normal**	No	High
Composite measure	Meets DETECT algorithm in patients with DLCO< 60% and disease duration of > 3 years	No	Moderate

*Symptoms: dyspnea on rest or exercise, fatigue, pre-syncope/ syncope, chest pain, palpitations, dizziness, lightheadedness.

Signs: Loud pulmonic sound, peripheral edema

**TTE without overt systolic dysfunction, greater than grade I diastolic dysfunction or greater than mild mitral or aortic valve disease or evidence of PH (as defined in TTE section)