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Screening and Diagnostic Modalities for Connective Tissue Diseases-Associated Pulmonary Arterial Hypertension: A Systematic Review

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Abstract

Objective—Pulmonary arterial hypertension (PAH) is a frequent complication in connective tissue diseases (CTD), especially in systemic sclerosis (SSc), and is associated with a high degree of morbidity and mortality. We undertook a systematic review for the screening tests for CTD-PAH.

Methods—A systematic literature search of PAH in CTD was performed in available databases through June 2012. Our evaluation of diagnostic tests was focused on patients with PAH confirmed by right heart catheterization (RHC).

Results—The search resulted in 2805 titles and 838 abstracts. Our final inclusion encompassed 21 manuscripts – 6 of which were case control studies and 15 were cohort studies. Twelve studies assessed the tricuspid regurgitation velocity (VTR) or equivalent right ventricular systolic pressure (RVSP) using transthoracic echocardiogram (TTE) as a threshold for RHC in patients suspected as having PAH. The screening threshold for RHC was VTR from >2.73 to >3.16 m/s without symptoms or 2.5 to 3.0 m/s with symptoms and resulted in 20–67% of patients having RHC proven PAH. Three studies looked at pulmonary function tests and found that a low lung diffusing capacity for carbon monoxide (DLCO) (45–70% of predicted) is associated with a 5.6–7.4% development of PAH, and a decline in DLCO% is associated with an increase in the specificity (for DLCO 60% spec= 45%, and for DLCO 50% spec=90%) for PAH. Five studies assessed N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) where a cut-off >239pg/ml has a sensitivity of 90–100%.

Conclusions—Our systematic review revealed that most evidence exists for TTE, pulmonary function tests, and NT-ProBNP for screening and diagnosis of SSc-PAH, however more robust studies are needed.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) in patients with connective tissue diseases (CTD) is common and ranges from 0.5% to 15% based on right heart catheterization (RHC) (1, 2). Currently, few guidelines exist for screening and diagnosis of pulmonary hypertension (PH) in CTD- except for guidelines that focused on pulmonary hypertension (PH) in general and all recommend yearly screening transthoracic echocardiogram (TTE) or TTE at the appearance of symptoms in SSc (3–5).

Cardiopulmonary involvement contributes to >50% of deaths in SSc patients (6, 7). Historically, CTD-PAH is associated with a poor prognosis, with a 1-year survival of 45% before development of PAH specific therapies. With current PAH therapies, SSc-PAH has a one year survival of 78% and a 3 year survival of 47% (8). The 3 year survival in PAH-SLE is more favorable and is estimated to be 75% (8). Pulmonary hypertension in CTD is often diagnosed at late stages with over 60% being diagnosed at functional class III or IV (9) and a recent study suggested that earlier diagnosis of SSc-PAH may lead to better survival (10). As part of an initiative to develop guidelines for screening and diagnosis of CTD-PAH(11), we conducted a systematic review to identify the best evidence for screening and diagnosis of PAH in CTD's. This systematic review provides comprehensive information for researchers and clinicians on screening and diagnosis of PAH.

METHODS

Structured Search Strategy

We searched PubMed, EMBASE, Web of science, and Scopus to find articles on PH and CTD with the help of an experience librarian (WT). Searches were conducted for literature published through June 19, 2012. In order to ensure a comprehensive search, no language or publication type limits were applied at the search strategy level. The Medline search strategy was conducted by combining selected keywords, medical subject headings, and the Clinical Queries search hedge for diagnostic clinical studies: (((("Diagnosis"[mesh] OR "diagnosis" [sh] OR "prevention and control"[sh] OR diagnost* OR diagnosi* OR diagnose* OR screen* OR "transthoracic echocardiogram" OR "pulmonary function test" OR "echocardiogram" OR "EKG" OR "chest radiograph" OR "N-terminal pro-brain natriuretic peptide" OR "NT-Pro-BNP" OR "NT-Pro BNP" OR (Diagnosis/Broad[filter]))) AND ("Hypertension, Pulmonary"[mesh] OR "pulmonary hypertension" OR "pulmonary arterial hypertension" OR (ayerza AND syndrome))) AND ("Connective tissue diseases"[mesh] OR "Collagen disease" OR "Collagen diseases" OR "Collagen vascular disease" OR "Connective tissue disease" OR "Connective tissue diseases" OR Dermatomyositis OR "Inflammatory myositis" OR Lupus OR "Mixed connective tissue disease" OR Polymyositis OR "Rheumatic disease" OR "Rheumatic diseases" OR "Rheumatoid arthritis" OR Scleroderma OR Sclerosis OR "Sjogren syndrome" OR Vasculitis). All search terms were exploded unless otherwise indicated. A unique search strategy was devised for each database to ensure appropriate utilization of keywords and relevant controlled vocabulary terms (MeSh terms in Medline, and Emtree headings in Embase). The full search strategies for all databases are available upon request. In addition, reviewers conducted hand-searches, including reference searching and cited-by searching, on relevant studies identified after application of inclusion and exclusion criteria. After de-duplication of the search results, 2805 unique citations were identified for review.

Selection of Instruments and Creation of Item Library

Under the supervision of the corresponding author (DK), HG and NA reviewed the citations generated from the search of PubMed, Scopus, Web of Science and Embase. The review

was divided into three stages: titles, abstracts, and manuscripts. Each generated title was assessed by two team members for relevancy, and was rejected if it fulfilled one of the following explicit exclusion criteria: 1) Not written in English, concerned with human subjects, or pertaining to adult studies; 2) Not pertaining to PAH or CTD; 3) Genetic studies or polymorphisms or diagnostic test or molecular/enzymatic mechanisms except serum/plasma biomarkers; 4) Articles related to treatment or prognosis of pulmonary hypertension; and 5) Editorials, letters, case reports, opinions, author reply or comments, etc.

If there were discordant assessments between reviewers, this was resolved during direct discussion between the two reviewers and, if there was uncertainty, included oversight by DK who reviewed and discussed the discordant titles. We were inclusive by accepting a title if there was uncertainty about how best to deliberate.

After a review of all 2805 (PubMed, EMBASE, SCOPUS and Web of Science) titles, 1967 titles were excluded by the application of the exclusion criteria – leaving 838 abstracts. We applied similar exclusion criteria to the 838 abstracts, with addition of the exclusion criteria detailed in Figure 1. Collectively, these criteria excluded 686 abstracts, and left a total of 152 manuscripts. Manuscripts were then divided into original studies and reviews. At this time we decided to only focus on original articles. We also reviewed systematic reviews on PAH in mixed connective tissue disease (MCTD) and PAH in SLE and pertinent review articles and handpicked 4 manuscripts. This led a total of 45 manuscripts. These 45 manuscripts were reviewed to determine if they represented PAH by RHC with clear exclusion of World Health Organization (WHO) group 2 (left heart disease) and WHO group 3 (interstitial lung disease [ILD]). If it was unclear, we contacted the corresponding authors (N=9) to clarify this. This resulted in the inclusion of 5 additional manuscripts in which authors confirmed the exclusion of WHO group 2 and 3 for a total of 21 PAH manuscripts for review. The exact terms, process and results of the search are summarized in Figure 1.

For all TTE, we converted the estimated right ventricular systolic pressure (RVSP) to tricuspid regurgitation velocity (VTR), since it was the most commonly reported parameter in the studies. Most studies included the estimated right atrial pressure (RAP), with the most common value of 10mmHg. For the three studies (12–14) that did not provide estimated RAP, we assumed a RAP of 10mmHg to calculate the VTR using the Bernoulli equation.

Quality Assessment

To evaluate the risk of bias and quality of our studies, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) evaluation tool (15). QUADAS assesses the risk of bias in 4 domains including patient selection, index test, reference standard and flow and timing. It also assesses applicability concerns for patient selection, index test and reference standard. Each of these seven components is evaluated with a set of questions to determine if the risk of bias is low, high or unclear. Studies receiving low risk in all domains are considered to have the highest quality.

RESULTS

Using the search strategy, of the 2,805 titles, 22 articles fulfilled the criteria for the RHC-defined PAH after excluding WHO group II (N=4) and III (N=16). Of these, 6 were case control studies and 16 were cohort studies (Appendix 1 and 2). A majority of our studies were cohort studies (16/22), and had a lower risk of bias or applicability concerns on QUADAS evaluation (Supplementary Table 1); 14/22 studies had low risk of bias or applicability concerns in all domains. The next few sections provide a summary of our search.

CARDIOLOGY MEASURES

Transthoracic Echocardiography—Twelve studies primarily evaluated TTE parameters for the diagnosis of PAH, of which 11 were cohort studies and 1 was a case control study. Eleven studies focused on SSc whereas one focused on SLE. The 10 SSc cohort studies (Table 1) had VTR cut offs ranging from 2.73–3.16 m/s without PAH-associated symptoms and 2.5–3.16 m/s with symptoms and PAH was found in 20–67% of patients who met criteria for RHC. Another cohort study by Ruiz-Irastorza in SLE patients used a VTR of 2.95 m/s with no mention of symptoms on 2 separate occasions which resulted in three patients going for RHC and none having PAH (16). In the one case control study, 15 SSc-PAH had mean VTR of 3.8 m/sec vs. 2.2 m/sec in SSc without PAH. (12).

Rajaram *et al.*'s cohort study of SSc patients at risk for PAH found that a dilated right ventricle on TTE had 49% sensitivity and 84% specificity for diagnosis of PAH (17). This study also looked at various VTR thresholds and showed that as the VTR threshold increased, the sensitivity decreased and specificity increased. A VTR >2.73m/s had a sensitivity 95% and specificity of 43%, whereas VTR >3.87 m/s had a sensitivity of 53% and a specificity of 100%.

Electrocardiograms (EKG)—One cohort study looked at EKG in 307 patients with CREST syndrome (now termed as limited cutaneous SSc [LcSSc]). Of these patients, 20 had RHC-PAH and concluded that right ventricle hypertrophy on EKG had sensitivity of 95% and specificity of 100% for PAH (18).

Cardiac Magnetic Resonance Imaging/Computed Tomography(MRI/CT)—

Rajaram *et al.* looked at 81 patients in a SSc cohort study, of which 55 (68%) were diagnosed with RHC-PAH and evaluated cardiac MRI and CT for diagnosis of SSc-PAH (17). On MRI, a right ventricle (RV) mass >30 grams had a sensitivity of 72% and specificity of 80% with a positive predictive value (PPV) of 91% and a likelihood ratio of 3.57. On CT, a cut-off pulmonary artery size 2.9 cm was found to have a sensitivity of 59%, specificity of 73%, and PPV of 87% with a likelihood ratio of 2.1 for detection of PAH.

PULMONARY MEASURES

Pulmonary Function Tests (PFT's)—Four studies looked at PFT's for screening for SSc-PAH. Three studies were cohort studies of SSc patients. The first cohort study looked at LcSSc patients using a cut-off diffusion capacity of the lung for carbon monoxide (DLCO) <45% of predicted (18), 307 patients underwent RHC of which 20 (6.5%) had PAH. The second study looked at DLCO/alveolar volume (DLCO/VA) <70% in 101 patients undergoing RHC of which 8 (7.4%) had PAH (19). The third cohort study looked at various DLCO parameters and found that as the DLCO threshold increased the sensitivity increased and the specificity decreased for diagnosis of PAH (sensitivity ranged from 39% to 74% for 50 to 60% DLCO percent predictive and specificity ranged from 45% to 90% (20))(20). The case control study evaluated the DLCO < 70.3 % and found a sensitivity of 93% and specificity of 100% whereas a forced vital capacity (FVC)/DLCO ratio 1.66 resulted in 64% sensitivity and 97% specificity (12). Combining a DLCO < 70.3% with a FVC/DLCO ratio 1.82 resulted in a sensitivity of 50% and specificity of 100%

Arterial oxygen partial pressure—Arterial oxygen partial pressure (PO₂) was examined in one cohort study and found that in 20 patients with LcSSc-PAH, the mean PO₂ was 64mmHg as compared to the 287 LcSSc patients without PAH that had a mean PO₂ of 76mmHg (p<0.01) (18).

Chest radiograph—One cohort study looked at right ventricle enlargement on chest x-ray as determined by a single radiologist and chest x-ray was 90% sensitive and 94% specific for the diagnosis of PAH(18).

LABORATORY VALUES

N-terminal pro B-type natriuretic peptide (NT-ProBNP)—Five studies (2 cohort studies and 3 case control studies) evaluated NT-ProBNP levels in SSc. The first cohort study used a cut-off NT-ProBNP > 236 pg/ml and found that it had a sensitivity of 45% and specificity of 90% for PAH(21). The second cohort study used a cut-off NT-ProBNP >97th percentile for age and found a sensitivity of 75% and specificity of 83% for diagnosis of PAH(19). With all studies including case-controls, a cut off >236pg/ml had a high specificity (83–100%) and a sensitivity ranging from 45–93% for diagnosis of PAH. 4/5 studies commented on the presence of normal NT-ProBNP values at time of diagnosis of PH, 3 of these studies reported 7–56% with PAH having normal NT-ProBNP.

Brain natriuretic peptide (BNP)—One cohort study evaluated BNP in SSc patients and found a high mean BNP in those who were subsequently diagnosed with PAH with a BNP cut off > 65 pg/ml had a 60% sensitivity and was 87% specific for SSc-PAH with a negative predictive value of 93% (21).

Erythrocyte sedimentation rate (ESR)—One study found a statistical difference ($p=0.0008$) in the mean ESR in SSc-PAH patients (33.7 mm/hour) as compared to SSc-No PAH (18.1 mm/hour) (19). A cut off > 28mm/hr was 50% sensitive and 85% specific for the diagnosis of PAH.

Autoantibodies and Disease Activity in SLE—We identified one case control study of 106 SLE patients without PAH and 41 SLE patients with PAH (22). This study showed a statistically significant higher prevalence of anti-U1RNP, and anti-cardiolipin antibodies in SLE-PAH as compared to SLE without PAH. This study also found a mean SLEDAI (a measure of disease activity) of 17.6 in SLE- PAH compared to 12.3 without PAH ($p < 0.05$) (22). In addition, Raynaud's phenomenon was statistically more prevalent in SLE patients with PAH as compared with SLE without PAH.

NAILFOLD CAPILLAROSCOPY

One case control study looked at 13 patients with SSc-PAH compared to 19 patients with SSc-NoPAH and found a statistically significant decrease in nailfold capillary density in those with PAH (4.33/mm) as compared to 6.56/mm in those without PAH(23).

DISEASE DURATION

One case-control study looked at 78 patients with SSc-PAH and found that PAH occurred at a mean of 6.3 (SD 6.6) years after the diagnosis of SSc (24). They showed that early onset PAH was just as frequent in those with diffuse SSc as compared to those with limited SSc.

COMPOSITE MEASURES

Four studies assessed the advantage of combining different screening tools. One case-control study used DLCO <70.3% and FVC/DLCO 1.82 and NT-ProBNP 209.8pg/ml, and found it was 100% sensitive and 100% specific for SSc-PAH (12). Another cohort study chose a DLCO/VA<70% and NT-ProBNP >97th percentile for age and found the combination to be 75% sensitive and 97% specific. Meune *et al* calculated the Cochin RPS score ($RPS=0.0001107(\text{age}) + 0.0207818 (150-\text{FVC}) + 0.04905 (100-\text{DLCO}/\text{alveolar volume})$) and reported that a cut off of 2.73 resulted in a sensitivity of 89.5 and specificity of

74.1% for PAH(14). In the DETECT study, 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 a two step algorithm: patients who met the first algorithm (based on clinical and laboratory parameters) would have a TTE as part of the second step of the algorithm and if they met this criteria, RHC was recommended resulting in a 96% sensitivity and 48% specificity for PAH (25).

Discussion

PAH is a frequent complication in patients with CTD, having the highest prevalence in SSc(26). Once patients develop PAH, they generally have a poor prognosis with a 1 year mortality greater than 20%(8). Although recent studies have shown that early diagnosis and treatment of PAH in these patients is key to improving survival (8), most patients are not diagnosed until functional class III or IV(9). As such, early diagnosis is needed to improve morbidity and mortality and pro-active screening is needed.

At present, only minimal guidelines exist for the screening and diagnosis of PAH, and those that are used are based on consensus opinion. For example, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend once yearly screening with Echocardiogram, however this was based upon consensus and a comprehensive literature review with minimal focus on CTD (4). The American College of Cardiology Foundation/American Heart Association also recommend yearly screening with echocardiogram for patients with CTD, but this recommendation was not evaluated for different subgroups of CTD, only used consensus opinion on the general topic of pulmonary hypertension, did not have a systematic review of the literature and was focused predominantly on echocardiogram with minimal mention of BNP or additional imaging and no mention of PFT's(3). None of these guidelines have been based on a systematic review of the literature and none have focused on CTD's.

CTD's appear to have different pathophysiology leading to the development of PAH. In SSc, PAH appears to occur due to intimal fibrosis and endothelial proliferation, whereas PAH in SLE may be multifactorial including vasculopathy, vasculitis or thromboembolic disease(27, 28). SSc is also felt to be a unique phenotype of PAH as shown from analysis of REVEAL(29) where SSc had the highest fatality in CTD-PAH.

Twelve studies assessed the VTR or equivalent RVSP using TTE as a threshold for RHC in patients suspected as having PAH. Eleven of these studies were in SSc, and one pertained to SLE. The screening threshold for RHC was VTR >2.73 to >3.16 m/s without symptoms or 2.5 to 3.0 m/s with symptoms. Of these studies, one study reported that VTR was unable to be estimated in 3/8 patients with PAH (30), and in 2 other studies(1, 31), VTR was unable to be estimated in 13–15% of the total cohort. In the remaining 9 studies the others did not provide the patients with an unmeasurable VTR. Although an exact threshold cannot be determined, the usefulness of TTE in screening for PAH was supported by our systematic review. In addition, for all patients with right atrial or right ventricular enlargement, RHC should be considered.

Previous guidelines have not addressed parameters other than TTE for screening for PAH. In our review, four studies assessed the use of PFT – focusing on percent predicted DLCO, FVC/DLCO ratio or DLCO/Va ratio for screening for PAH. Various DLCO cut offs were used ranging from <45% to < 70%. These studies suggest that there is likely a utility of using PFT's for screening of PAH, however the varying inclusion criteria and varying cut-off parameters with only a modest specificity, requires additional studies in order to make an accurate recommendation. Five studies assessed NT-ProBNP for screening and diagnosis of

PAH in CTD, and for cut-offs >236pg/ml and there was a specificity of 83–100% for RHC-PAH. This suggests that NT-ProBNP will likely prove to be a useful tool in screening for PAH.

For all other screening modalities, limited studies exist. Rajaram et al.(17) looked at CT and MRI of the heart which both appeared useful in his study; however these tests would not be feasible in all centers and is currently considered as a research tool. The other modalities including nailfold capillarscopy, ESR, and autoantibodies in SLE require larger cohort studies.

In our literature review, a majority of the data was in SSc, with only a few manuscripts on SLE or MCTD. On final inclusion of RHC only PAH there were only 2 studies on SLE and none for MCTD. This underscores the need to systematically study these diseases. Also, the estimates for prevalence is uncertain for PAH in MCTD and ranges from 5% on RHC to as high as 23% in a study of 47 MCTD patients who were diagnosed by RHC or at autopsy (32, 33). For SLE, PAH prevalence on RHC is estimated at 0.5% and up to 14% when diagnosed by TTE(34, 35).

We only focused on studies that used RHC to diagnose PAH. We decided to exclude studies that define PH using TTE or other non-invasive modalities. TTE is a good screening tool but can under-or, over-estimate the sPAP (31, 36). In addition, up to 28% of patients with SSc-PAH may not have a measurable VTR(37). The sensitivity and specificity of a test is based on every patient undergoing the gold standard (RHC here) in order to pick up any false negative from the screening test. This was accurately captured in only 4 manuscripts (17, 20, 25, 38). In addition, each of these manuscripts also had inclusion/exclusion criteria based on the screening tests making it impossible to calculate true sensitivity and specificity with RHC as the gold standard. Also, our review could have been bolstered by a meta-analysis of the TTE parameters. However, due to varying inclusion criteria and the inability to determine true negatives and false negatives in majority of the studies, we were unable to perform a meta-analysis.

In conclusion, our systematic review suggests that majority of research and work has been performed in SSc. Most evidence exists for the use of TTE, PFT's and NT-ProBNP for the screening and diagnosis of PAH in SSc. The lack of true negatives and false negatives in these studies confirms the need for more robust studies. Further studies are also needed to evaluate the utility of screening tools in other CTD's.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Systematic Review Schematic

¹ Exclusion Criteria

1. Not written in English, concerned with human subjects, or pertaining to adult studies
2. Not pertaining to pulmonary arterial hypertension or connective tissue diseases.
3. Genetic studies or polymorphisms or molecular/enzymatic mechanisms except serum/plasma biomarkers.
4. Articles related to treatment or prognosis of pulmonary hypertension.
5. Editorials, letters, case reports, opinions, author reply or comments, etc.

² Exclusion Criteria

1. Does not have an abstract, unless a review article.
2. Not a case control or cohort study, or a case-control or cohort study with $n < 20$ patients with connective tissue disease Not pertaining to pulmonary arterial hypertension or elevated pulmonary artery pressure.
3. Not pertaining to connective tissue disease.
4. Genetic studies or polymorphisms or diagnostic test or molecular/enzymatic mechanisms
5. Editorials, letters, case reports, opinions, author reply or comments, etc. Except review articles after 2008 pertaining to pulmonary hypertension and connective tissue disease screening and diagnosis.
6. Not having right heart catheterization to diagnose PAH.

³ Exclusion Criteria

1. Review article.
2. Pertaining to exercise-induced PAH only

3. Pertaining to pre-PAH such borderline PAH
4. Discussing prognosis, treatment response only
5. For case-control: does not have appropriate comparator (such as CTD without PH)
6. Does not exclude ILD or left heart disease

⁴ Hand Picked

Table 1

TTE VTR- COHORTS

Author	Parameter Cut off	Number with suspected PH undergoing RHC	RHC proven PAH N (%)
1. Phung, 2009	VTR >2.73 or 2.5–2.73 m/s with symptoms	44	24 (55%)
2. Jansa, 2012	VTR >2.73m/s **	17	6 (35%)
3. Ciurzynski, 2010	VTR >2.8/m/s at rest and/or >1.58 m/s increase with exercise **	16	2 (12.5%)
4. Hachulla, 2005	VTR >3m/s or 2.5–3m/s with symptoms	33	14 (42%)
5. Hachulla, 2009	VTR >3m/s or 2.5–3m/s with symptoms	26	6 (23%) + 2 additional with exercise PH
6. Launay, 2007	VTR 3.16 m/s **	32	12 (38%)
7. Hinchcliff, 2011	VTR >2.5 Δ $\dagger$ * and DLCO <55% predicted, FVC/DLCO 1.6	87	49 (57%)
8. Avouac, 2010	VTR >2.73 m/s or DLCO < 50% w/o ILD or unexplained dyspnea $\dagger$	206	42 (20%)
9. Allamore, 2008	VTR>2.73 m/s, DLCO <50% in absence of ILD, unexplained dyspnea and r/o thromboembolic $\dagger$	19	8 (42%)
10. Rajaram, 2012	VTR 3.16, VTR 2.73–3.16 with DLCO <50% or unexplained dyspnea Δ **	81	54 (67%)
11. Ruiz-Irastorza, 2012 (SLE)	VTR 2.95 m/s (on 2 separate TTE) and VTR > 3 $\dagger$ (RAP 5mmHg)	3	0 (0%)

VTR= tricuspid regurgitation velocity

$\dagger$ Converted from systolic pulmonary artery pressure (sPAP) to VTR

* Assumed RAP =10mmHg

** Converted TRG to VTR

Δ Inclusion criteria for the cohort $\dagger$ Incident cohort