Combination of Echocardiographic and Pulmonary Function Test Measures Improves Sensitivity for Diagnosis of Systemic Sclerosis-associated Pulmonary Arterial Hypertension: Analysis of 2 Cohorts

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ABSTRACT. ***Objective***. To evaluate routinely collected non-invasive tests from 2 systemic sclerosis (SSc) cohorts to determine their predictive value alone and in combination versus right heart catheterization (RHC)-confirmed pulmonary arterial hypertension (PAH).

Methods. We evaluated 2 cohorts of patients who were at risk or with incident PAH: (1) The Pulmonary Hypertension Assessment and Recognition Outcomes in Scleroderma (PHAROS) cohort and (2) an inception SSc cohort at Cochin Hospital, Paris, France. Estimated right ventricular systolic pressure (eRVSP) as determined by transthoracic echocardiogram (TTE) and pulmonary function test (PFT) measures was evaluated, and the predictive values determined. We then evaluated patients with PAH missed on TTE cutoffs that were subsequently identified by a PFT measure.

Results. In the PHAROS cohort (n = 206), 59 (29%) had RHC-defined PAH. An eRVSP threshold of 35–50 mm Hg failed to diagnose PAH in 7% to 31% of patients, 50% to 70% of which (n = 2–13) were captured by PFT measures. In the Cochin cohort (n = 141), 10 (7%) patients had RHC confirmed PAH. An eRVSP threshold of 35-50 mm Hg missed 0% to 70% (n = 0–7) of patients, of which 0% to 68% (n = 0–6) were met by PFT measures. The combination of TTE and PFT improved the negative predictive value for diagnosing PAH.

Conclusion. In 2 large SSc cohorts, screening with TTE and PFT captured a majority of patients with PAH. TTE and PFT complement each other for the diagnosis of PAH. (First Release Aug 15 2013; J Rheumatol 2013;40:1706–11; doi:10.3899/jrheum.130400)

Key Indexing Terms:
ECHOCARDIOGRAM PULMONARY FUNCTION TESTS SYSTEMIC SCLEROSIS
PULMONARY HYPERTENSION DIAGNOSIS PULMONARY ARTERIAL HYPERTENSION

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Dr. Khanna was supported by a grant from NIH/NIAMS K24AR063120, is on the speakers bureau for Actelion and United Therapeutics, and is a consultant for Actelion, Bayer, BMS, DIGNA, Genetech/Roche, Gilead, InterMune, Merck, Sanofi, and United Therapeutics. Dr. Steen has received funding from Gilead Science for support of the PHAROS study and is on the speakers bureau for Actelion and Gilead.

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Accepted for publication June 6, 2013.

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Pulmonary arterial hypertension (PAH) affects 5% to 15% of patients with systemic sclerosis (SSc) and is a leading cause of mortality[1,2,3]. A metaanalysis of 3818 patients showed a prevalence of PAH of 9% (95% CI 6%–12%) and identified advanced age, longer disease duration, and limited cutaneous disease subset as risk factors for this condition[4]. Humbert, *et al* recently showed improved survival in patients with PAH who were proactively screened and treated early during the course of their disease[2]. However, the diagnosis of PAH is challenging as the symptoms (dyspnea at rest or with exertion, lower extremity edema, fatigue, dizziness, and palpitations) usually overlap with other SSc-related manifestations (musculoskeletal involvement, deconditioning, lung fibrosis), often leading to a delayed or missed diagnosis[5]. Current guidelines for PAH screening recommend transthoracic echocardiogram (TTE) in patients with SSc once yearly or when symptoms first occur[6,7,8], but do not refer to other screening modalities. Right heart catheterization (RHC) remains the gold standard for diagnosis of PAH with demonstration of a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg and a pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg[9].

At present, only consensus-based guidelines exist for the screening and diagnosis of SSc-PAH. The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend once yearly screening with TTE[6]. The American College of Cardiology Foundation/American Heart Association also recommend yearly screening of patients with connective tissue disease (CTD) for PAH with TTE, but this recommendation was not evaluated for different subgroups of CTD[10]. The lack of CTD or SSc-specific evidence based guidelines and the frequency of PAH in patients with SSc support the importance of defining better screening and diagnosis methods.

We used 2 large cohorts of patients with SSc that were initially recruited with the goal of detecting patients at high risk of SSc-PAH. Our analysis had 3 primary objectives: (1) To assess the predictive values of estimated right ventricular systolic pressure (eRVSP) on TTE and pulmonary function test (PFT) measures [ratio of forced vital capacity percentage predicted to DLCO percentage predicted (FVC%/DLCO%); DLCO% predicted cutoffs]; (2) to identify patients who test positive by PFT measures but are missed by eRVSP cutoffs; and (3) to assess predictors of PAH in the 2 cohorts when accounting for patient demographics, serum autoantibodies, eRVSP, and pulmonary function tests (FVC%/DLCO% ratio and DLCO% predicted).

MATERIALS AND METHODS

Study population. We analyzed data on patients enrolled in a prospective study — the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort — as of May 2009[11,12]. PHAROS is a collaborative, multicenter study based in North America. It was established to prospectively follow 2 groups of patients with SSc (n = 206) (defined according to the American College of Rheumatology classification)[13]; those with PAH confirmed by RHC and those considered at high-risk for developing PAH[11]. The entry criteria for patients at high risk for PAH were one of the following: (1) DLCO < 55% predicted without severe interstitial lung disease (ILD); (2) FVC% predicted/DLCO% predicted ratio greater than 1.6; and (3) eRVSP > 40 mm Hg on TTE. Patients with pulmonary hypertension (PH) were excluded if the left ventricular ejection fraction (LVEF) was < 50%, to exclude left sided systolic heart failure, or the PH was caused by other cardiopulmonary disease, drugs, or toxins. Patients with PH on RHC were divided into World Health Organization (WHO) groups 1, 2, and 3[14]. Group 1 PH (or PAH) was defined by RHC hemodynamics of mPAP ≥ 25 mm Hg and PCWP ≤ 15 mm Hg with an FVC ≥ 70% predicted and none to mild ILD on high resolution CT. Patients in Groups 2 and 3 were excluded from the analysis.

The second cohort of 141 SSc patients consists of a prospective cohort of consecutive patients enrolled in the Paris Cochin Rheumatology cohort (Cochin cohort) aimed at evaluating SSc patients for PAH. Patients that had an eRVSP > 40 mm Hg on TTE, or DLCO < 50% predicted in the absence of pulmonary fibrosis, or unexplained dyspnea underwent RHC for diagnosis of PAH.

Baseline demographics from both cohorts included age, SSc subtype [limited cutaneous systemic sclerosis (lcSSc) or diffuse cutaneous SSc (dcSSc)], race (white vs non-white), time since diagnosis (first non-Raynaud sign or symptom), autoantibody profile [anti-centromere antibody (ACA) and anti-topoisomerase antibody (ATA)], FVC%/DLCO%, DLCO% predicted, and eRVSP measures. ACA and ATA were done in the commercial laboratories in the PHAROS cohort. ACA was done by using immunofluorescence on HEP2 Cells and ATA was done by using counter immune-electrophoresis in the Cochin cohort. Neither cohort had exclusion criteria for SSc specific medications. TTE was performed as part of routine clinical care.

Statistical analysis. The PHAROS and Cochin cohorts were each evaluated alone and in combination. Student t tests were conducted to determine any statistical difference between the 2 cohorts. In order to compare patients with RHC-confirmed PAH to those without RHC-PH, we examined the sensitivity, specificity, and positive predictive values (PPV) and negative predictive values (NPV) of eRVSP, FVC%/DLCO%, and DLCO% predicted using various thresholds. Since one of the goals of our study was to identify optimal screening tests, we also assessed the NPV of TTE and PFT measures combined. Patients with RHC-confirmed PAH were also evaluated based on eRVSP, and the number of patients that were not detected as having PAH was computed to determine how useful various PFT measures are in detecting PAH.

Finally, to determine the baseline demographic factors, autoantibodies, TTE, and PFT results that can be used to diagnose and predict PAH, we ran univariate and multivariate logistic regressions on the 2 cohorts combined[15]. Findings were considered indicative of statistical significance if $p < 0.05$.

RESULTS

The PHAROS cohort had 206 patients compared to 141 in the Cochin cohort. The mean age of patients was 57.2 years (SD 11.6, $p < 0.01$) in the PHAROS cohort as compared to 53.7 years (SD 11.8, $p < 0.01$) in the Cochin cohort (Table 1). In the PHAROS cohort, patients had longer disease duration (7.1 yrs vs 4.7 yrs, $p < 0.01$), and only 14% were ATA positive compared to 32% in the Cochin cohort ($p < 0.01$).

In the PHAROS cohort, 59 subjects had WHO Class I PAH, 34 had PH secondary to ILD, 37 had PH secondary to left heart disease, 55 had no PH, and 21 patients could not be classified due to either missing FVC% predicted or

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Table 1. Baseline data for the PHAROS and Cochin databases.

	PHAROS (n = 206)	Cochin (n = 141)	p	PHAROS PAH (n = 59)	Cochin PAH (n = 10)	p
Age, yrs, mean (SD)	57.2 (11.6)	53.7 (11.8)	< 0.01	62.4 (10.3)	63.1 (12.9)	0.87
Female, %	85.1	84.0	0.78	88.0	60.0	0.08
lcSSc, %	62.6	56.0	0.22	78.0	60.0	0.27
White, %	69.6	93.0	< 0.01	83.0	100.0	< 0.01
ACA+ (%)	21.0	22.0	0.82	41.0	20.0	0.14
ATA+ (%)	14.0	32.0	< 0.01	5.0	50.0	< 0.01
Time since diagnosis (yrs), mean (SD)	7.1 (8.1)	4.7 (6.7)	< 0.01	8.0 (10.1)	9.9 (8.6)	0.53
Non-RP symptom (yrs), mean (SD)	8.7 (7.3)	NA	NA	9.4 (8.9)	NA	NA
DLCO%, mean (SD)	40.6 (16.1)	71.3 (20.6)	< 0.01	43.1 (17.8)	38.6 (7.8)	0.19
FVC% predicted, mean (SD)	74.7 (20.1)	94.0 (20)	< 0.01	87.9 (12.95)	82.6 (10.4)	0.16
eRVSP (mm Hg), mean (SD)	53.0 (21)	31.6 (9.9)	< 0.01	61.5 (20.2)	49.5 (6.8)	< 0.01

PAH: pulmonary arterial hypertension; lcSSc: limited cutaneous systemic sclerosis; ATA: anti-topoisomerase antibody; ACA: anti-centromere antibody; RP: Raynaud phenomenon; FVC: forced vital capacity; eRVSP: estimated right ventricular systolic pressure.

missing PCWP data. This left 114 patients for current analysis (PAH [n = 59] and without PH [n = 55]). We excluded patients with PH secondary to left heart disease or secondary to ILD from analysis. In the Cochin cohort (n = 141), 10 subjects had WHO Class I PAH, 5 had ILD-PH, 2 had PH secondary to left heart disease, and 124 were without PH. The current analysis included 134 patients (10 with PAH and 124 without PH). In patients with PAH (Table 1), the average eRVSP was lower in the Cochin cohort than in the PHAROS cohort (49.5 mm Hg vs 61.5 mm Hg, $p < 0.01$) and more were ATA positive (50% vs 5%, $p < 0.01$).

The eRVSP on TTE and PFT (FVC%/DLCO%, DLCO%) were analyzed to determine the ability of various cutoffs to accurately predict PAH (Table 2). When combining the 2 cohorts, an eRVSP of > 35 mm Hg resulted in a 58% PPV and 97% NPV compared to an eRVSP > 50 mm Hg that resulted in an 85% PPV and 87% NPV (Table 2). As the eRVSP threshold increased, the NPV decreased, resulting in more cases of PAH being missed by eRVSP screening alone.

We also evaluated 2 PFT measures (DLCO% predicted and the FVC%/DLCO% ratio) because of their known associations with PAH[16,17,18,19] (Table 2). In the 2 cohorts, a ratio of FVC%/DLCO% ≥ 1.6 had a 47% PPV and a 90% NPV, whereas a ratio of FVC%/DLCO% ≥ 2.0 had a 65% PPV and an 85% NPV. For DLCO% predicted in the 2 cohorts, DLCO% < 60% resulted in a 47% PPV and a 92% NPV (Table 2).

Because eRVSP had the highest PPV (Table 2), we determined the proportion of patients with RHC-PAH who were missed when using eRVSP cutoffs but fell within the PFT measures (Table 3). In the PHAROS cohort, 55 (93%) of the 59 patients with RHC-PAH had an eRVSP > 35 mm Hg and 4 (7%) had eRVSP ≤ 35 mm Hg. Of the 4 patients missed, 2 (50%) were identified by DLCO-predicted < 60% or FVC%/DLCO% ratio ≥ 1.6. In the Cochin cohort, however, there were only 10 patients with RHC-PAH, of which 100% were identified by an eRVSP > 35 mm Hg. As the eRVSP threshold increased, the number of patients with RHC-PAH that were missed increased simultaneously. Using as criteria

Table 2. Positive and negative predictive values of transthoracic echocardiogram (TTE) and pulmonary function tests (PFT) at detecting pulmonary arterial hypertension (PAH).

	PHAROS, n = 114				Cochin, n = 134				All, n = 248			
	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec
eRVSP > 35 mm Hg	0.63	0.85	0.93	0.42	0.38	1.0	1.0	0.87	0.58	0.97	0.94	0.73
eRVSP > 40 mm Hg	0.69	0.79	0.85	0.60	0.71	1.0	1.0	0.97	0.70	0.94	0.87	0.85
eRVSP > 45 mm Hg	0.74	0.75	0.78	0.71	0.83	0.96	0.50	0.99	0.75	0.90	0.74	0.91
eRVSP > 50 mm Hg	0.84	0.72	0.69	0.85	1.0	0.95	0.30	1.0	0.85	0.87	0.64	0.96
FVC%/DLCO% ≥ 1.6	0.53	0.52	0.80	0.24	0.30	0.99	0.90	0.83	0.47	0.90	0.81	0.65
FVC%/DLCO% ≥ 1.8	0.56	0.56	0.71	0.40	0.38	0.98	0.80	0.90	0.52	0.88	0.72	0.74
FVC%/DLCO% ≥ 2.0	0.68	0.62	0.61	0.69	0.50	0.97	0.60	0.95	0.65	0.85	0.61	0.87
DLCO% < 70	0.50	0.25	0.90	0.04	0.18	1.0	1.0	0.63	0.39	0.93	0.91	0.45
DLCO% < 60	0.50	0.38	0.83	0.11	0.36	1.0	1.0	0.85	0.47	0.92	0.86	0.63
DLCO% < 50	0.55	0.56	0.75	0.35	0.50	0.99	0.90	0.93	0.54	0.89	0.77	0.75

PPV: positive predictive value; NPV: negative predictive value; Sens: sensitivity; Spec: specificity; eRVSP: estimated right ventricular systolic pressure in mm Hg; FVC/DLCO: forced vital capacity/DLCO percent predicted ratio.

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Table 3. Patients captured by transthoracic echocardiogram (TTE) and pulmonary function test (PFT) measurements in the 2 cohorts.

eRVSP on TTE, mm Hg	Total Number of Patients Meeting TTE Criteria	Patients Missed by TTE Threshold, n (%)	Patients Missed by TTE and Identifed by DLCO < 60, n (%)	Patients Missed by TTE and Identified by Ratio ≥ 1.6, n (%)
PHAROS	n = 59			
> 35	55	4 (7)	2 (50)	2 (50)
> 40	50	9 (15)	7 (78)	7 (78)
> 45	46	13 (22)	9 (69)	9 (69)
> 50	41	18 (31)	12 (67)	13 (72)
Cochin	n = 10			
> 35	10	0 (0)	0 (0)	0 (0)
> 40	10	0 (0)	0 (0)	0 (0)
> 45	5	5 (50)	5 (100)	4 (80)
> 50	3	7 (70)	7 (100)	6 (86)

eRVSP: estimated right ventricular systolic pressure in mm Hg; FVC/DLCO: forced vital capacity/DLCO percent predicted ratio.

eRVSP > 50 mm Hg, 18 (31%) patients in the PHAROS cohort with RHC-PAH were missed, of which 12 (67%) were identified by DLCO-predicted < 60% and 13 (72%) were identified by FVC%/DLCO% ratio ≥ 1.6. In the Cochin cohort, 7 (70%) patients were missed using eRVSP > 50 mm Hg; however, they were all identified when DLCO-predicted < 60% was used.

We developed a matrix of TTE and PFT measures to assess if combination would improve the NPV (Table 4). By combining both TTE and PFT measures, we were able to improve the NPV over eRVSP or PFT measures alone. With an eRVSP > 50 mm Hg, 36% of patients with PAH were missed; however, a combination of eRVSP > 50 mm Hg with FVC%/DLCO% ≥ 1.6 captured 91% of patients (Table 4).

We next evaluated baseline demographics, clinical laboratory results, eRVSP, ratio of FVC%/DLCO%, or DLCO% predicted for their ability of predicting PAH. For this goal, we fit a univariate logistic regression model (outcome variable: PAH vs no PH) on the combined database comprising the 2 cohorts (n = 248). A positive ACA increased the odds of having PAH, as well as having a greater FVC%/DLCO% ratio and having eRVSP > 40 mm Hg (Table 5). In contrast, the presence of ATA decreases the likelihood of having PAH (Table 5). In the multivariate logistic regression model (PAH vs no PH), the significant predictors for PAH were eRVSP > 40 mm Hg (OR 29.2; 95% CI 11.2, 76.3; and the ratio of FVC%/DLCO% ≥ 1.6; OR: 2.89; 95% CI for OR 1.12, 7.46) after adjusting for age, disease duration, ACA, and ATA (Table 6).

DISCUSSION

Patients with SSc have a high risk of developing PAH, and current guidelines recommend a TTE on a yearly basis or at the appearance of symptoms in SSc[6,7]. Several cohort studies have suggested an eRVSP cutoff of 40 mm Hg (with calculated tricuspid velocity of 2.73-3.0 m/s, assuming right atrial pressure of 5–10 mm Hg), should be referred for RHC[20,21,22,23]. However, TTE can be nonspecific and can overestimate or underestimate the eRVSP on RHC[24,25]. As such, better, more predictive noninvasive tests or combinations of tests are needed to screen patients.

Previous studies looked at a combination of noninvasive measures for the diagnosis of PAH. However, none evaluated the combination of PFT and TTE or PPV and NPV of PFT and TTE for PAH. In a prospective study, Meune, *et al*[26] proposed a composite score using PFT along with patient age to estimate the risk of SSc patients developing PAH within 3 years. They developed the Cochin risk prediction score (RPS) and validated it in a separate prospective study of 443 patients. In that study, a Cochin

Table 4. Positive and negative predictive values of combination of transthoracic echocardiogram (TTE) and pulmonary function test (PFT) measurements.

	eRVSP > 35 mm Hg				eRVSP > 40 mm Hg				eRVSP > 45 mm Hg				eRVSP > 50 mm Hg			
PFT measurements	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec
FVC%/DLCO% ≥ 1.6	0.433	0.978	0.970	0.512	0.508	0.982	0.970	0.638	0.508	0.966	0.940	0.649	0.513	0.951	0.910	0.669
FVC%/DLCO% ≥ 1.8	0.455	0.980	0.970	0.551	0.546	0.984	0.970	0.689	0.553	0.969	0.940	0.707	0.560	0.948	0.896	0.730
FVC%/DLCO% ≥ 2.0	0.492	0.982	0.970	0.615	0.643	0.986	0.970	0.793	0.655	0.947	0.882	0.822	0.687	0.937	0.851	0.851
DLCO < 60%	0.436	0.978	0.970	0.517	0.500	0.982	0.970	0.626	0.500	0.965	0.940	0.649	0.508	0.966	0.940	0.649
DLCO < 70%	0.369	0.969	0.970	0.362	0.406	0.975	0.970	0.454	0.403	0.963	0.955	0.454	0.408	0.964	0.955	0.465

eRVSP: estimated right ventricular systolic pressure in mm Hg; FVC/DLCO: forced vital capacity/DLCO percent predicted ratio; PPV: positive predictive value; NPV: negative predictive value; Sens: sensitivity; Spec: specificity.

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Table 5. Univariate logistic regression for association with pulmonary arterial hypertension (PAH).

	n	OR (95% CI)	p
Age	247	1.08 (1.05, 1.1)	< 0.001
Female	247	0.8 (0.4, 1.7)	0.58
SSc disease duration	244	1.06 (1.0, 1.1)	0.001
ACA	236	2.78 (1.5, 5.2)	0.001
ATA	235	0.41 (0.2, 0.9)	0.03
TTE (continuous)	241	1.17 (1.1, 1.2)	< 0.001
FVC%/DLCO% (continuous)	246	4.93 (2.8, 8.6)	< 0.001
eRVSP > 40 mm Hg	241	40.28 (17.7, 91.8)	< 0.001
FVC%/DLCO% ≥ 1.6	246	8.19 (4.2, 16.1)	< 0.001

ACA: anti-centromere antibody; ATA: anti-topoisomerase antibody; TTE: transthoracic echocardiogram in mm Hg; eRVSP: estimated right ventricular systolic pressure; FVC%/DLCO%: forced vital capacity/DLCO percent predicted ratio.

Table 6. Multivariate logistic regression for association with pulmonary arterial hypertension (PAH).

	OR (95% CI)	p
Age	1.04 (0.996, 1.09)	0.07
SSc disease duration	0.99 (0.93, 1.05)	0.78
ACA	1.54 (0.53, 4.42)	0.43
ATA	0.53 (0.16, 1.79)	0.31
eRVSP > 40 mm Hg	29.34 (11.26, 76.41)	< 0.001
FVC%/DLCO% ≥ 1.6	2.98 (1.16, 7.66)	0.02

ACA: anti-centromere antibody; ATA: anti-topoisomerase antibody; eRVSP: estimated right ventricular systolic pressure; FVC%/DLCO%: forced vital capacity/DLCO percent predicted ratio.

RPS of 2.73 had a 90% sensitivity and 74% specificity in detecting patients who developed PAH during followup[26]. In another prospective cohort study, Allanore, *et al* combined the ratio of DLCO to alveolar volume < 70% with N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) level > 97th percentile for age and found the combination to be 75% sensitive and 97% specific for PAH[27]. In a case-control study, the authors used DLCO-predicted < 70.3%, FVC%/DLCO% ≥ 1.82, and NT-ProBNP ≥ 209.8 pg/ml and found them to be 100% sensitive and 100% specific for SSc-PAH[18]. A recently published prospective study assessed PFT in combination with laboratory values and clinical characteristics in a stepwise algorithm, with a cutoff score prompting TTE[28] and subsequent TTE cutoffs prompting RHC for screening of RHC-PAH.

Our study looked at 2 cohorts and found that the combination of eRVSP on TTE and PFT measures resulted in the detection of up to 97% to 100% of patients with RHC confirmed PAH. This is a vast improvement over using TTE alone for screening and early detection of PAH. Additionally, these criteria allowed for the detection of 31% to 70% of patients who were missed using an eRVSP > 50 mm Hg, but were later confirmed with RHC. The selected PFT measures were chosen based on published studies suggesting that FVC%/DLCO% ratio > 1.6 or DLCO predicted < 60% are strongly associated with PAH[16,18,28]. Our data also confirm that FVC%/DLCO% ratio > 1.6 is a reasonable cutoff for screening for PAH as it has a higher NPV than higher cutoff values[18,28].

Early diagnosis and treatment of PAH in SSc patients is essential for an improved prognosis. Our results suggest that by using both TTE and PFT, patients with PAH can be identified with simple and worldwide available tests. By using both modalities, patients at risk of PAH are more likely to be identified by one of the noninvasive tests, thus providing better rationale for RHC to confirm PAH and initiate treatment.

Our study has many strengths. Our study calculated predictive values of TTE and PFT in 2 large SSc cohorts, which has not been done in pure PAH cohorts. Mukerjee, *et al* evaluated both PFT and TTE for the diagnosis of PH; however, TTE results did not exclude patients with ILD[16].

Our study is not without limitations. The PHAROS database did not have routine collection of NT-ProBNP or brain natriuretic peptide, which have been shown to be predictive for PAH[29,30] in SSc. In addition, we focused only on eRVSP on TTE, since we did not have additional TTE data, including tricuspid pulmonic gradient or tricuspid annular plane systolic excursion (TAPSE) or right chamber enlargement, both shown to be associated with PAH. Mathai, *et al* evaluated TAPSE in SSc-PAH and found that it is a sensitive and reproducible measure of RV function and was associated with other measures of RV function in a large cohort[31].

We have shown that screening with TTE and PFT identified the majority of patients with SSc-PAH. TTE and PFT complement each other for the diagnosis of SSc-PAH. We recommend the use of both TTE and PFT for screening of SSc-PAH.

REFERENCES

1. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66:940-4.
2. Humbert M, Yaici A, de Groote P, Montani D, Sitbon O, Launay D, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011;63:3522-30.
3. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology 2012;51:1017-26.
4. Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290-8.
5. Hegewald MJ, Markewitz B, Elliott CG. Pulmonary hypertension: clinical manifestations, classification and diagnosis. Int J Clin Pract Suppl 2007 Sep;156:5-14.

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6. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219-63.
7. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation 2009;119:2250-94.
8. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55-66.
9. Hoeper MM. Definition, classification, and epidemiology of pulmonary arterial hypertension. Semin Respir Crit Care Med 2009;30:369-75.
10. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573-619.
11. Bae S, Saggar R, Bolster MB, Chung L, Csuka ME, Derk C, et al. Baseline characteristics and follow-up in patients with normal haemodynamics versus borderline mean pulmonary arterial pressure in systemic sclerosis: results from the PHAROS registry. Ann Rheum Dis 2012;71:1335-42.
12. Hinchcliff M, Fischer A, Schiopu E, Steen VD; PHAROS Investigators. Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): baseline characteristics and description of study population. J Rheumatol 2011;38:2172-9.
13. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.
14. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43-54.
15. Jupiter DC. Logistic models — an odd(s) kind of regression. J Foot Ankle Surg 2013;52:279-80.
16. Mukerjee D, St George D, Knight C, Davar J, Wells AU, Du Bois RM, et al. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. Rheumatology 2004;43:461-6.
17. Steen V, Medsger TA, Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. Arthritis Rheum 2003;48:516-22.
18. Thakkar V, Stevens W, Prior D, Moore OA, Byron J, Liew D, et al. N-terminal pro-brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case-control study. Arthritis Res Ther 2012;14:R143.
19. Stupi AM, Steen VD, Owens GR, Barnes EL, Rodnan GP, Medsger TA, Jr, et al. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. Arthritis Rheum 1986;29:515-24.
20. Jansa P, Becvar R, Ambroz D, Palecek T, Tomcik M, Skacelova S, et al. Pulmonary arterial hypertension associated with systemic sclerosis in the Czech Republic. Clinical Rheumatol 2012;31:557-61.
21. Vachiery JL, Coghlan G. Screening for pulmonary arterial hypertension in systemic sclerosis. Eur Respir Rev 2009;18:162-9.
22. Phung S, Strange G, Chung LP, Leong J, Dalton B, Roddy J, et al. Prevalence of pulmonary arterial hypertension in an Australian scleroderma population: screening allows for earlier diagnosis. Intern Med J 2009;39:682-91.
23. Hsu VM, Moreyra AE, Wilson AC, Shinnar M, Shindler DM, Wilson JE, et al. Assessment of pulmonary arterial hypertension in patients with systemic sclerosis: comparison of noninvasive tests with results of right-heart catheterization. J Rheumatol 2008;35:458-65.
24. Ciurzynski M, Bienias P, Pruszczyk P. Should patients with connective tissue disease undergo exercise Doppler echocardiography? Chest 2010;138:1523-4; author reply 1524.
25. Hachulla E, de Groote P, Gressin V, Sibilia J, Diot E, Carpentier P, et al. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum 2009;60:1831-9.
26. Meune C, Avouac J, Airò P, Beretta L, Dieudé P, Wahbi K, et al. Prediction of pulmonary hypertension related to systemic sclerosis by an index based on simple clinical observations. Arthritis Rheum 2011;63:2790-6.
27. Allanore Y, Borderie D, Avouac J, Zerkak D, Meune C, Hachulla E, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum 2008;58:284-91.
28. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2013 May 18 [Epub ahead of print].
29. Cavagna L, Caporali R, Klersy C, Ghio S, Albertini R, Scelsi L, et al. Comparison of brain natriuretic peptide (BNP) and NT-proBNP in screening for pulmonary arterial hypertension in patients with systemic sclerosis. J Rheumatol 2010;37:2064-70.
30. Allanore Y, Borderie D, Meune C, Cabanes L, Weber S, Ekindjian OG, et al. N-terminal pro-brain natriuretic peptide as a diagnostic marker of early pulmonary artery hypertension in patients with systemic sclerosis and effects of calcium-channel blockers. Arthritis Rheum 2003;48:3503-8.
31. Mathai SC, Sibley CT, Forfia PR, Mudd JO, Fisher MR, Tedford RJ, et al. Tricuspid annular plane systolic excursion is a robust outcome measure in systemic sclerosis-associated pulmonary arterial hypertension. J Rheumatol 2011;38:2410-8.

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