# Assessment of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis: Comparison of Noninvasive Tests with Results of Right-Heart Catheterization

VIVIEN M. HSU, ABEL E. MOREYRA, ALAN C. WILSON, MEIR SHINNAR, DANIEL M. SHINDLER, JULIANNE E. WILSON, AMI DESAI, and JAMES R. SEIBOLD

***ABSTRACT.*** ***Objective.*** Pulmonary hypertension (PH) is an ominous complication in patients with scleroderma (systemic sclerosis, SSc). We compared noninvasive assessment of PH with pulmonary artery (PA) pressures obtained by right-heart catheterization (RHC).

***Methods.*** Forty-nine patients with SSc were evaluated for suspected PH based on clinical findings, progressive dyspnea, and pulmonary function tests (PFT). PH was defined as mean PA pressure ≥ 25 mm Hg, or ≥ 30 mm Hg after exercise, with normal pulmonary capillary wedge pressure (PCW). Doppler echocardiography (echo) and cardiac magnetic resonance imaging (MRI) were performed within 4 hours of RHC, and the predictive accuracy of the tests was compared.

***Results.*** RHC identified 24/49 (49%) patients with PH. The noninvasive cutpoints were: estimated right ventricular systolic pressure > 47 mm Hg by echo; diameter of the main PA > 28 mm by MRI; and the ratio of forced vital capacity to diffusion capacity (%FVC/%DLCO) > 2.0 by PFT. Echo classified 38 subjects correctly (14/24 with and 24/25 without PH; sensitivity 58%, specificity 96%). The area under receiver-operating characteristic curve (AUC) was 0.84 for echo. MRI measurement of PA diameter had a sensitivity of 68% and specificity 71% (AUC 0.78). PFT evaluation had a sensitivity of 71% and specificity of 72% (AUC 0.76).

***Conclusion.*** In evaluation of SSc with suspected PH, echo appeared to be the most useful among the noninvasive tests, mainly due to the high specificity, high positive predictive value, and highest AUC. However, due to the low sensitivity of noninvasive testing, RHC should remain the gold standard. (First Release Jan 15 2008; J Rheumatol 2008;35:458–65)

*Key Indexing Terms:*

PULMONARY ARTERIAL HYPERTENSION — SYSTEMIC SCLEROSIS
DOPPLER ECHOCARDIOGRAPHY — CARDIAC MAGNETIC RESONANCE IMAGING
PULMONARY FUNCTION TEST — RIGHT-HEART CATHETERIZATION

Lung disease is the leading cause of morbidity and mortality in patients diagnosed with scleroderma or systemic sclerosis (SSc)[1,2]. Fifteen to twenty percent of patients with SSc are afflicted by significant pulmonary hypertension (PH), with a median survival of 1.5–2 years[3]. PH as seen in SSc can occur as (1) isolated pulmonary artery (PA) hypertension, frequently found in patients with limited cutaneous scleroderma[4,5], or (2) complicating interstitial lung disease (ILD), frequently associated with the diffuse cutaneous scleroderma[2,6]. The contribution from either ILD or PH to dyspnea may vary from patient to patient and may coexist with other factors such as left ventricular diastolic dysfunction. Subtle symptoms and physical findings of pulmonary involvement can be missed and consequently a patient may present with advanced signs of right-heart failure and an ominous prognosis[1,7]. Thus, timely identification of pulmonary involvement in patients with scleroderma has assumed great importance.

Right-heart catheterization (RHC) remains the definitive test in the diagnosis of PH[8]. However, it is impractical as a screening test because it is invasive; therefore various noninvasive studies have been proposed as useful screening tests for PH in SSc[9,10]. The goal of our study was to assess the

*From the University of Medicine and Dentistry of New Jersey Scleroderma Program; Division of Cardiovascular Diseases and Hypertension, UMDNJ Robert Wood Johnson Medical School, New Brunswick, New Jersey; Yale University, New Haven, Connecticut; and University of Michigan, Ann Arbor, Michigan, USA.*

*V.M. Hsu, MD, Assistant Professor, Director, Scleroderma Program; J.E. Wilson, RN, BSN, Research Coordinator, UMDNJ Scleroderma Program; A.E. Moreyra, MD, Professor; A.C. Wilson, PhD, Associate Professor; M. Shinnar, MD, Associate Professor, Director, Cardiac MRI; D.M. Shindler, MD, Professor, Medical Director, Echocardiography, Division of Cardiovascular Diseases and Hypertension, UMDNJ Robert Wood Johnson Medical School; A. Desai, MD, Yale University; J.R. Seibold, MD, Professor, Director, Scleroderma Program, University of Michigan, Ann Arbor.*

*Address reprint requests to Dr. V.M. Hsu, UMDNJ Scleroderma Program, Clinical Research Center, Acute Care Bldg., 3rd floor, PO Box 19, New Brunswick, NJ 08903-0019. E-mail: hsuvm@umdnj.edu*

*Accepted for publication October 15, 2007.*

reliability of 3 noninvasive tests, Doppler echocardiography (echo), cardiac magnetic resonance imaging (MRI), and pulmonary function studies (PFT), in the diagnosis of PH in patients with SSc. There are no published data evaluating these 3 methods in diagnosing PH secondary to SSc. If the information provided by these tests is shown to be accurate and reliable, then their application would be important in the daily management of these patients.

## MATERIALS AND METHODS

*Subjects.* We performed a prospective review of established or new patients who presented consecutively to the UMDNJ-Scleroderma Program between 2002 and 2004 with progressive dyspnea and/or had clinical features suspicious of PH. These features included: a loud pulmonic component of the second heart sound, results of screening noninvasive cardiac testing by prior echo-Doppler if PA systolic pressure > 40 mm Hg, or PFT (reduced DLCO resulting in elevated FVC/DLCO ratio > 1.4). Results from PFT were considered if obtained within 6 months of the RHC. These patients (total of 55 patients) underwent a clinical protocol that included cardiac MRI, echo-Doppler, and RHC as part of their PH evaluation during the same admission. Informed consent was obtained for the procedures. Permission was obtained from the UMDNJ Institutional Review Board for the chart review and data analysis.

All patients were above 18 years of age and met the American College of Rheumatology classification criteria for SSc or its spectrum of related connective tissue diseases[11]. This spectrum included diffuse scleroderma, limited scleroderma, calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasias (formerly known as the CREST syndrome)[12], and the overlap syndrome of SSc with another rheumatic illness such as polyarthritis or myopathy. Patients were excluded if they had left ventricle dysfunction by echo or RHC, airway obstruction by PFT, thromboembolic pulmonary hypertension (excluded by V/Q scan), congenital heart disease, porto-pulmonary PH, or HIV, and those who refused RHC or cardiac MRI. Six of the 55 subjects were excluded for elevated resting pulmonary capillary wedge (PCW > 15 mm Hg), leaving 49 subjects for analysis.

*RHC procedure.* RHC was performed by percutaneous approach via the femoral vein using a 7-French Swan-Ganz catheter (Edwards Lifesciences). Baseline pressures were recorded in the right atrium, right ventricle, PA, and PCW position. Cardiac output was obtained by thermodilution technique in triplicate and the average value was used. Blood samples from the right atrium and PA were drawn for oxygen saturation to exclude shunts. Recording of PA pressures, heart rate, and cardiac output measurements was repeated after an exercise challenge using 5-pound dumbbells in each hand that the patient raised in a semicircular fashion above the chest for 5 min or until onset of fatigue. Most patients completed at least 2 min exercise time.

PH was defined as a mean PA pressure measured by RHC $\geq$ 25 mm Hg at rest or $\geq$ 30 mm Hg with exercise, with a PCW $\leq$ 15 mm Hg[8,13,14].

*Echo study.* Echo images were obtained using a Philips Sonos 7500 model. Tricuspid regurgitant flow velocity was measured by continuous-wave echo with both an imaging probe and a non-imaging Pedoff pencil probe. No contrast enhancement was given. Right ventricular systolic pressure (RVSP) was estimated from the peak tricuspid regurgitant flow velocity (v, in m/s) using a modified Bernoulli equation, $P = 4v^2 + 10$, where P represents the pressure in mm Hg. All echo-Doppler studies were read by a single reader.

*Cardiac MRI.* Images were obtained on a Philips CVMR system (Philips Medical Systems, Eindhoven, The Netherlands) equipped with Master gradients (30 mT/m, and slew rate 150 T/m/s) and a 5-channel synergy cardiac coil. The 2 measures examined in this study were the dilation of the main PA in mm ($PA_{diam}$) and the maximum blood flow velocity in the PA in cm/s ($PA_{vmax}$).

*Cutpoints.* All data analysis and plots were performed using SAS® version 8.2 software (SAS Institute, Cary, NC, USA). A linear regression procedure was used to compute cutpoints for echo-Doppler, cardiac MRI, and PFT measures. Figure 1 illustrates scatterplots and regression lines including the correlation coefficients (adjusted $r^2$). Horizontal lines show the cutpoints, corresponding to the mean PA pressure at rest of 25 mm Hg measured by RHC for $PA_{diam}$, and peak flow velocity $PA_{vmax}$ measured by MRI, estimated RVSP measured by echo-Doppler, and the FVC/DLCO ratio by pulmonary function testing.

The Logistic procedure was used to compare the rates of false-positives and false-negatives at different cutpoints and to produce receiver-operating characteristic (ROC) curves to compare the predictive accuracy of the tests as described by the area under the curve (AUC). Final cutpoints were adjusted to minimize false-negatives. Comparisons of proportions used the chi-square test; p values < 0.05 were considered significant.

## RESULTS

*Patients.* The demographic data of the study group are shown in Table 1. The proportions of limited SSc and diffuse SSc were similar; only 4 patients (8%) had an overlap syndrome. The duration of SSc disease until time of PH evaluation ranged from 2 to 27 years (mean 10 yrs). Significant ILD involving at least 25% of the lung (lower zones) was confirmed in 42/49 patients (86%) by high-resolution computerized tomography (HRCT) scan of the chest. This correlated with reduction in percentage total lung capacity (TLC) < 80% measured by PFT in 95% of cases. The average mean PA pressure measured at RHC was 25.3 mm Hg (range 11–58 mm Hg). Twenty-four patients met criteria for PH (Table 2) using the mean PA pressure definition either at rest or with exercise. Twelve of 16 patients with PH at rest and 6 of 8 with PH during exercise had concomitant ILD. There were 5 patients with isolated PAH and negligible ILD.

*Echo results.* Figure 1A shows the regression line between mean PA pressure at rest and estimated RVSP by echo. The estimated RVSP cutpoint is 47 mm Hg. This cutpoint was able to correctly identify 38 subjects (14 true-positives and 24 true-negatives; 58% sensitivity, 96% specificity) and had a high positive predictive value (PPV), 93% (Table 3). The AUC by ROC analysis was 0.84 for estimated RVSP (Figure 2).

Other echocardiographic findings included evidence of enlarged right-side chambers in 8 patients (all but one had PH) and small pericardial effusions. Four subjects had significant pericardial effusions, but none of these patients had echocardiographic signs of cardiac tamponade.

*Cardiac MRI.* Forty-nine patients underwent the MRI study. Figure 1B shows the regression line between mean PA pressure and the diameter of the main PA. The PA diameter cutpoint corresponding to mean PA pressure of 25 mm Hg was 28 mm (Table 3). This cutpoint was able to correctly identify 34 subjects (17 true-positives and 17 true-negatives; 68% sensitivity, 71% specificity). The negative predictive value (NPV) was 68%. The AUC by ROC analysis was 0.78 for this measure (Figure 2).

There is an inverse relationship between PA blood flow

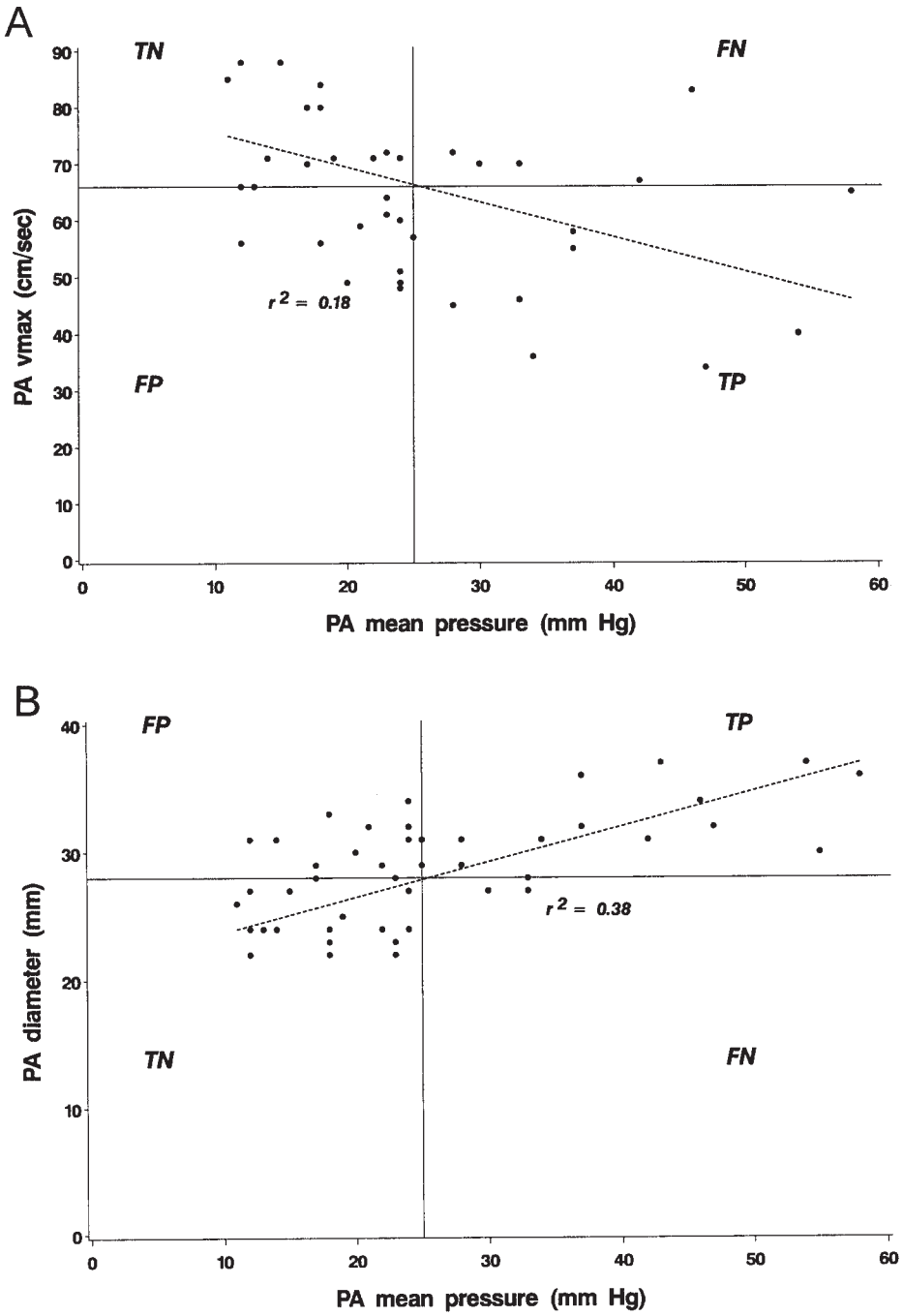


*Figure 1.* Scatterplots and regression lines showing cutpoints corresponding to PH defined as PA pressure ≥ 25 mm Hg at rest measured by right-heart catheterization in 49 patients with scleroderma. A. PA $v_{max}$, cutpoint < 66 cm/s. B. PA diameter, cutpoint > 28 mm. FN: false-negative, FP: false-positive, TN: true-negative, TP: true-positive.

velocity and PA pressure, as seen in the regression line between mean PA pressure and the maximum blood velocity in the PA. The velocity cutpoint corresponding to mean PA pressure of 25 mm Hg was 66 cm/s. This cutpoint was able to correctly identify 24 subjects out of 42 with velocity measurements (12 true-positives and 12 true-negatives; 57% sensitivity, 57% specificity). The NPV was 57%. The AUC by ROC analysis was 0.70 for this measure (Figure 2).

*PFT results.* Figure 1D shows the regression line between mean PA pressure and FVC/DLCO by pulmonary testing. A mean PA pressure of 25 mm Hg corresponds to a PFT estimated FVC/DLCO ratio of 2.

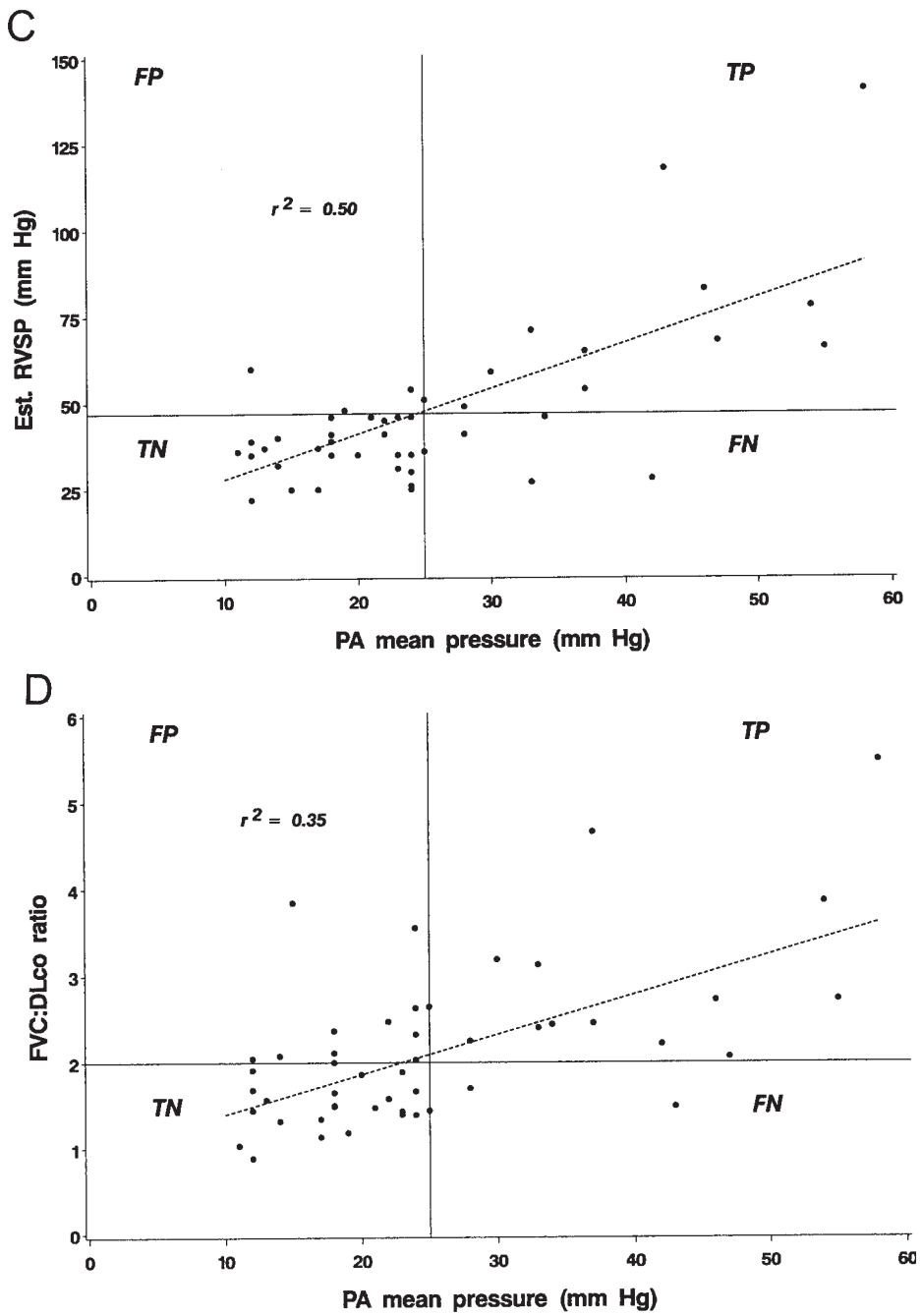


*Figure 1.* C. Estimated RVSP, cutpoint > 47 mm Hg. D. FVC/DLCO ratio, cutpoint > 2. Adjusted correlations $r^2$ values are shown. FN: false-negative, FP: false-positive, TN: true-negative, TP: true-positive.

Thirteen patients with a ratio > 2 had PH by RHC criteria (71% sensitivity, 72% specificity; Table 3). The NPV was 72%. The AUC by ROC analysis was 0.76 (Figure 2).

## DISCUSSION

In this series of patients with scleroderma, we found that noninvasive assessment of PH had shortcomings, with different degrees of sensitivity and specificity. This pattern of inconsistency required RHC to confirm or dismiss the diagnosis of PH with certainty.

We found that echo served as the most reliable method to diagnose PH when the estimated RVSP was > 47 mm Hg (PPV 93%). This method had the highest positive likelihood ratio (14.6) of all the tests studied (Table 3), and also had the greatest area under the ROC curve (Figure 2). A lower RVSP cutoff (such as RVSP 40 mm Hg) could serve better to increase the sensitivity (83%) of this test, should echo-

Doppler be used solely for PH screening, although specificity would be reduced to 76%.

Echo has been proposed as a screening tool to diagnose elevated pulmonary arterial pressure[10]. In addition, it is considered to be useful in assessing right atrium and ventricle size and function as well as evaluating left-side valvular disease, a cause of secondary PH[15]. The assessment of PA pressure by this test relies on measurement of the tricuspid regurgitation jet to provide an indirect measurement of the systolic PA pressure (RVSP). The absence of this jet does not exclude PH and there is significant variability among investigators in technique and interpretation of results. Studies of the reliability of echo have shown that this technique may be negatively affected by the presence of concomitant lung disease, and we observed similar findings[16-19]. Poor acoustic window due to lung disease or body habitus or changes in chest wall configuration and cardiac orientation may contribute to the disparity. The combination of pulmonary hypertension and pulmonary fibrosis in SSc is not well studied to date, and this large group of patients is often excluded from clinical trials. Chang, *et al*[20] reported increased mortality in their SSc patients with combined disease, similar to those with isolated pulmonary hypertension. Mukerjee, *et al*[21] found positive predictive accuracy of echocardiography and DLCO obtained from pulmonary functions to be adequate for the diagnosis of advanced PH, but neither test could be relied on to exclude PH.

Echo missed the diagnosis in 42% (10/24) of our PH population, although 6 of the 10 false-negatives had exercise-induced PH. Eight patients who met RHC PH criteria with exercise but not at rest had borderline RVSP values by echo, which lay close to the cutoff of 47 mm Hg, and more than half also had significant ILD. The exercise portion of the RHC was not standardized completely and this could be a limitation of our study, since many patients completed less

*Table 1.* Demographic and clinical characteristics of patients referred for pulmonary hypertension.

| Patient Characteristics | Study Group |
|---|---|
| N | 49 |
| Age, yrs, mean (range) | 55 (20–80) |
| Sex, % (female/male) | 82/18 |
| Race, % (White/Black) | 76/24 |
| Scleroderma type, % | |
| Limited scleroderma | 49 |
| Diffuse scleroderma | 43 |
| Other | 8 |
| Disease duration, yrs, mean (range) | 10 (2–27) |

*Table 2.* Summary of noninvasive test results in scleroderma patients with pulmonary hypertension by right-heart catheterization criteria.

| | | Doppler Echo | Right-Heart Catheterization Hemodynamics | | | | Pulmonary Function Test | | | Cardiac MRI | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient | Disease Type | Estimated RVSP | PA Sys/Dia, mm Hg | Mean $PAP_{rest}$ ($PAP_{ex}$), mm Hg | $PCW_{rest}$ ($PCW_{ex}$) | CO, l/min | % FVC/ % DLCO | Ratio FVC/DLCO | % TLC | PA Diameter, mm | PA Maximum Velocity, cm/s |
| 1 | L | 36 | 37/15 | 25 | 13 | 5.8 | 82/31 | 2.6 | 68 | 29 | NA |
| 2 | D | 46 | 53/19 | 34 | 9 | 4.5 | 61/25 | 2.4 | 66 | 31 | 36 |
| 3 | L | 118 | 68/25 | 43 | 5 | 4.4 | 64/43 | 1.5 | 76 | 37 | 36 |
| 4 | L | 83 | 74/28 | 46 | 8 | 5.0 | 117/43 | 2.7 | 89 | 34 | 83 |
| 5 | D | 59 | 44/18 | 30 | 13 | 5.1 | 83/26 | 3.2 | 92 | 27 | 70 |
| 6 | L | 49 | 41/18 | 28 | 14 | 5.3 | 68/40 | 1.7 | 75 | 29 | 45 |
| 7 | L | 78 | 89/30 | 54 | 7 | 4.0 | 85/22 | 3.9 | 69 | 37 | 40 |
| 8 | L | 48 | 47/16 | 31 | 7 | 5.8 | 62/30 | 2.1 | 84 | 32 | 34 |
| 9 | L | 65 | 60/21 | 37 | 2 | 5.4 | 42/9 | 4.7 | 36 | 32 | 58 |
| 10 | D | 54 | 64/22 | 37 | 3 | 5.4 | 54/22 | 2.5 | 55 | 36 | 55 |
| 11 | D | 51 | 47/14 | 25 | 8 | 2.7 | 39/21 | 1.9 | 39 | 31 | 57 |
| 12 | L | 28 | 70/23 | 42 | 11 | 7.6 | 93/42 | 2.2 | 98 | 31 | 67 |
| 13 | L | 141 | 90/33 | 58 | 9 | 5.7 | 33/6 | 5.5 | 47 | 36 | 65 |
| 14 | D | 41 | 47/16 | 28 | 12 | 10.7 | 72/32 | 2.3 | 70 | 31 | 72 |
| 15 | L | 71 | 52/20 | 33 | 14 | 4.7 | 72/83 | 0.87 | 77 | 27 | 46 |
| 16 | L | 66 | 85/36 | 55 | 10 | 5.0 | 71/26 | 2.7 | NA | 30 | NA |
| 17 | L | 41 | 34/13 | 22 (49) | 3 (3) | 5.8 | 94/38 | 2.5 | 69 | 29 | 71 |
| 18 | L | 46 | 36/10 | 21 (41) | 12 (17) | 5.1 | 87/59 | 1.5 | 72 | 32 | 59 |
| 19 | L | 54 | 41/17 | 24 (39) | 9 (9) | 5.9 | 107/46 | 2.3 | 93 | 27 | 60 |
| 20 | D | 46 | 38/15 | 24 (36) | 11 (12) | 5.4 | 96/27 | 3.6 | 81 | 34 | 49 |
| 21 | L | 48 | 28/12 | 19 (36) | 12 (15) | 4.6 | 78/66 | 1.2 | 94 | 25 | NA |
| 22 | L | 35 | 34/16 | 23 (37) | 10 (16) | 8.9 | 53/37 | 1.4 | 43 | 28 | 72 |
| 23 | D | 27 | 37/12 | 23 (32) | 9 (11) | 5.2 | 60/25 | 2.4 | 56 | 28 | 70 |
| 24 | L | 45 | 33/13 | 22 (35) | 11 (13) | 7.7 | 79/50 | 1.6 | 78 | 24 | NA |

D: diffuse scleroderma, L: limited scleroderma. RVSP: right ventricular systolic pressure; PA: pulmonary artery; PAP: pulmonary arterial pressure; PCW: pulmonary capillary wedge pressure; TLC: total lung capacity; NA: not available.

*Table 3.* Performance statistics of noninvasive tests compared to pulmonary hypertension determined by right-heart catheterization criteria.

| Test (Measure) | Cutpoint | ROC AUC (95% CI) | TP, FP FN, TN | PPV/NPV, % | Sensitivity, Specificity, % | + LR/–LR |
|---|---|---|---|---|---|---|
| MRI, PA diameter | > 28 mm | 0.78 (0.65–0.91) | 17, 7 8,17 | 71/68 | 68/71 | 2.3/0.45 |
| MRI, PA velocity | < 66 cm/s | 0.70 (0.55–0.86) | 12, 9 9, 12 | 57/57 | 57/57 | 1.3/0.75 |
| Echo, estimated RVSP | > 47 mmHg | 0.84 (0.72–0.95) | 14, 1 10, 24 | 93/71 | 58/96 | 14.6/0.43 |
| PFT, FVC/DLCO ratio | > 2.0 | 0.76 (0.62–0.90) | 17, 7 7, 18 | 71/72 | 71/72 | 2.5/0.41 |

Echo: Doppler echocardiography; PFT: pulmonary function test; ROC AUC: area under the receiver-operating characteristic curve; PPV: true-positive/all positives; NPV: true-negative/all negatives; sensitivity: true-positive/true-positive + false-negative (FN); specificity: true-negative/true-negative + false-positive (FP); + LR: positive likelihood ratio (sensitivity/1– specificity); – LR: negative likelihood ratio (1–sensitivity/specificity); TP: true-positive; FP: false-positive; TN: true-negative; FN: false-negative.

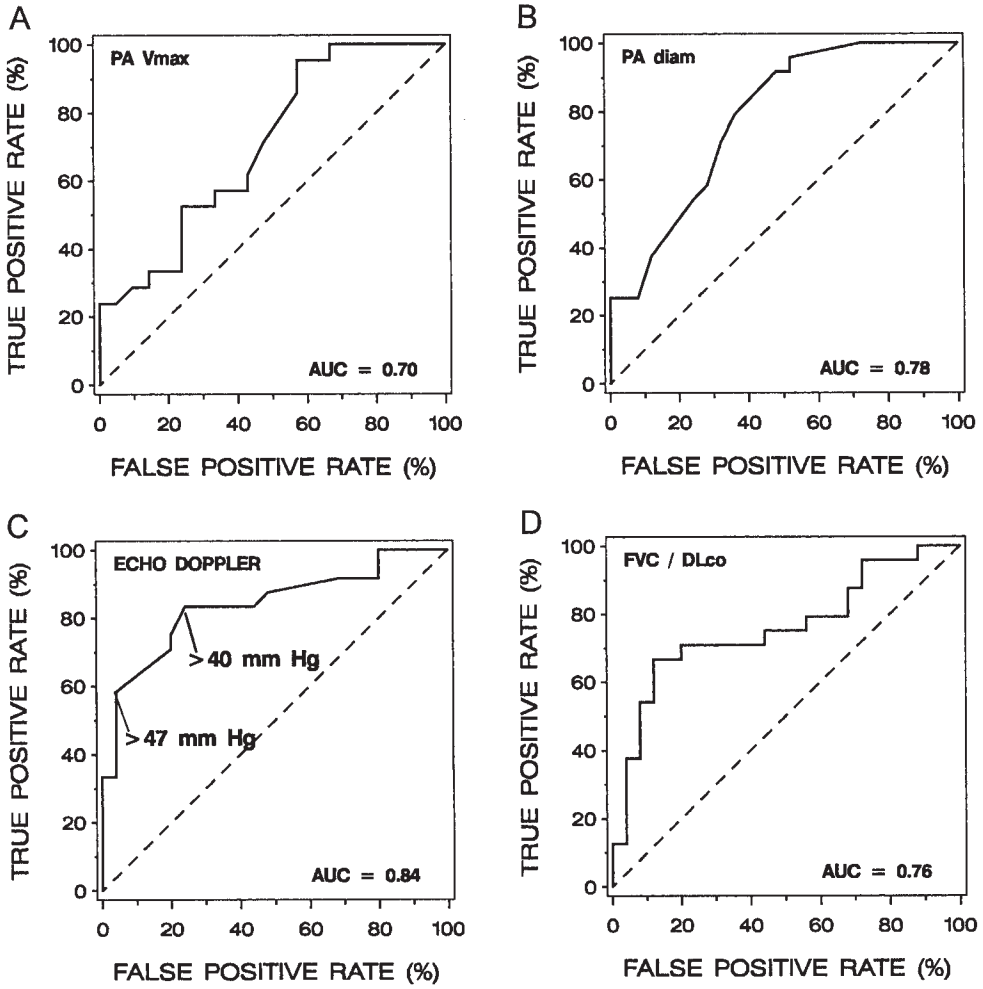


*Figure 2.* Receiver-operating characteristic curves for the diagnosis of PH in patients with scleroderma using cardiac MRI, PA $v_{max}$, PA diameter, Doppler echocardiography-estimated RVSP, and pulmonary function testing FVC/DLCO ratio. PH was defined as PA pressure ≥ 25 mm Hg at rest, or PA pressure ≥ 30 mm Hg with exercise, measured by right-heart catheterization. Areas under the curves (AUC) were calculated by the trapezoidal rule.

than 3 minutes of exercise before onset of fatigue. Whether an exercise echo would have detected this condition remains unknown. Nevertheless, the clinical course in this group is unclear and prospective studies are under way to determine whether this group will eventually meet PH criteria at rest. Two of these patients, Patients 18 and 22, had mild elevation of PCW during exercise. This small elevation in PCW pressure during exercise has been described in elderly patients and in those with a rapid heart rate response[22], and does not necessarily reflect LV dysfunction. It is important to differentiate these patients from others with exercise-induced PH because prostanoid therapy would be contraindicated in patients with severe left ventricular systolic dysfunction[23-28].

Cardiac MRI has been proposed for screening or following SSc-related PH[29,30]. The usefulness of cardiac MRI in the evaluation of PH has also been studied previously in primary pulmonary hypertension, but not in the setting of concomitant ILD. Marcus, *et al*[23] studied 12 patients with primary pulmonary hypertension by MRI, and described abnormal septal bowing in early diastole when right ventricular pressure exceeded the left ventricular pressure by > 5 mm Hg. In several other studies of primary pulmonary hypertension, agreement between MRI and RHC was variable[29,31]. We found the PA diameter measurement and pulmonary flow velocity determined by MRI were less sensitive and specific, yielding more false-positives than echo-Doppler testing. The likelihood ratios associated with the velocity determination were close to 1.0, indicating a low degree of usefulness (Table 3).

Pulmonary function testing is very useful in characterizing underlying airway or parenchymal disease of the lung. An isolated reduction in DLCO is a frequent abnormality in SSc and a DLCO < 55%, or a ratio of FVC (% predicted)/DLCO (% predicted) > 1.4, is reported to be strongly associated with PH[3]. Serial DLCO testing has been recommended in screening scleroderma patients for PH, although a reduced DLCO is not specific for PH and can be seen in ILD and emphysema. We found a statistically significant correlation between mean PA pressure by RHC and elevated FVC/DLCO ratio, suggesting that PFT should be included in the initial evaluation of dyspnea when considering PH. Using the FVC/DLCO ratio > 2 identified more subjects with PH than echo-Doppler study. Although PFT is a good screening test for SSc-related lung disease, with a balance of sensitivity and specificity, it misclassified 8 of the 24 patients with PH in this series, predominantly in the group with exercise-induced PH. Among 15 patients with very low total lung capacity (%TLC < 60% and DLCO < 45%) who had diffuse pulmonary fibrosis with honeycombing confirmed by HRCT scan and moderate to severe dyspnea, only 5 were confirmed to have PH by RHC.

The predictive value of these noninvasive tests may be enhanced by combining the results. For example, no patient having all normal values (below the cutpoints) for echo-Doppler, PFT ratio, and MRI PA diameter had PH confirmed by RHC. Thus RHC may not be necessary when all 3 noninvasive tests are found to be below the cutpoints.

A limitation of our study is that at a referral center, screening bias may have selected the sickest patients and the population may not truly represent the scleroderma community at large. Significant PH is thought to affect 15%–20%[20] of the scleroderma community. The magnitudes of the positive likelihood ratios of individual noninvasive tests are not sufficiently greater than 1.0 to give acceptable PPV in populations with PH prevalence typical of the SSc community (for example, a typical prevalence of 15% yields a PPV of only 36% using echo-Doppler). However, the negative likelihood ratio for the echo-Doppler test is 0.43, which would increase the NPV to 98% in a typical SSc community.

Future studies may be needed to evaluate other techniques that may alter the results, including more specialized echo tests such as tissue Doppler, strain rate imaging, pharmacologic stress testing with dobutamine, and TAPSE (tricuspid annular plane systolic excursion), which may enhance the usefulness of noninvasive testing as a diagnostic approach. Other cardiac MRI variables that could have altered the results, such as right ventricular structure and function, should be included in future trials.

We conclude that individually, noninvasive testing in the assessment of PH in patients with SSc has limited value. Echo-Doppler appeared to be the most useful, mainly due to the high PPV. A combination of noninvasive tests (echo, MRI, and PFT) offers better predictive value. RHC should remain the gold standard in the initial evaluation of PH.

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