Prevalence of Pulmonary Hypertension in Limited and Diffuse Scleroderma*

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Study objectives: To characterize the prevalence of undiagnosed pulmonary hypertension in patients with limited and diffuse scleroderma.

Design: Prospective cross-sectional study.

Setting: University-based outpatient clinic.

Patients: Thirty-four consecutive patients with limited (n=29) or diffuse (n=5) scleroderma but without the clinical diagnosis of pulmonary hypertension.

Measurements and results: All patients had 12-lead ECGs and two-dimensional and Doppler echocardiograms. The pulmonary artery systolic pressure (PAS) was calculated as the sum of the Doppler tricuspid pressure gradient and the right atrial pressure as estimated by the caval respiratory index. Thirty-three patients (97%) had adequate spectral signals of tricuspid regurgitation. The velocity of tricuspid regurgitation ranged from 1.6 to 4.5 m/s. The calculated PAS ranged from 15 to 95 (mean±SD=30±14 mm Hg). Twelve patients (35% of the total cohort) had pulmonary hypertension defined as PAS of 30 mm Hg or greater.

Conclusions: Undiagnosed elevation of PAS is common in patients with scleroderma. Noninvasive assessment of PAS can be performed accurately in most patients independent of clinical signs of pulmonary hypertension. If successful treatment strategies are identified, it may be possible to identify patients early in the development of pulmonary hypertension and intervene before significant end-organ damage occurs.

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Key words: diagnosis; pulmonary hypertension; scleroderma

Abbreviations: CREST=calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, telangiectasias; Dco=diffusing capacity of carbon monoxide; PAS=pulmonary artery systolic pressure

Scleroderma, characterized as limited or diffuse, is notable for a high prevalence of pulmonary involvement with abnormalities found in up to 70% of patients at autopsy.1 Abnormalities in pulmonary function are present in most patients and include reductions in diffusing capacity, restrictive abnormalities, and airway obstruction.2-4 Pulmonary involvement represents a major cause of morbidity and mortality in these patients.5-7 However, premortem diagnosis of pulmonary involvement is often difficult because of minimal symptoms, unremarkable findings on physical examinations, and normal chest radiographs.5

The reported rates of pulmonary hypertension in patients with scleroderma have been wide ranging with estimates as low as 0% in patients with the diffuse variant8 to as high as 60% in patients with limited scleroderma (formerly called the CREST syndrome inclusive of calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias).9 These earlier studies were retrospective in design and depended on autopsy or surgical specimens, thus introducing an inherent bias by including patients with more advanced disease.

Doppler echocardiography has emerged as a reliable and reproducible means of noninvasively assessing pulmonary artery systolic pressure (PAS),10-13 and has been employed to detect pulmonary hypertension in patients with connective tissue diseases. Simonson et al14 used Doppler echocardiography to detect pulmonary hypertension in patients with systemic lupus erythematosus and reported a prevalence rate of 14%. Others have specifically studied patients with scleroderma.15,16 These studies included patients with overt pulmonary disease15 or employed relatively low-sensitivity Doppler techniques (<40%) for measuring pulmonary pressures.16 Accordingly, the present investigation was designed to assess the prevalence of pulmonary hypertension in patients with scleroderma but without a previous diagnosis of pulmonary hypertension.
Table 1—Baseline Clinical Characteristics (n=34)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Age, yr mean±SD</td>
<td>53±12</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>32 (94)</td>
</tr>
<tr>
<td>Limited disease</td>
<td>29 (85)</td>
</tr>
<tr>
<td>Diffuse disease</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Tobacco exposure</td>
<td>15 (44)</td>
</tr>
<tr>
<td>Symptoms (PND, DOE, orthopnea)</td>
<td>22 (65)</td>
</tr>
<tr>
<td>RAE or RVH</td>
<td>2 (6)</td>
</tr>
<tr>
<td>RV heave, increased P2 or JVP</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Vasodilators at time of testing</td>
<td>18 (53)</td>
</tr>
<tr>
<td>Vasodilator therapy</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

*DOE=dyspnea on exertion; JVP=jugular venous pressure; P2=pulmonic closure sound; PND=paroxysmal nocturnal dyspnea; RAE=right atrial enlargement; RV=right ventricular; RVH=right ventricular hypertrophy.

**Materials and Methods**

**Patients**

Patients were prospectively identified from the Rheumatology Practice at the University Health Center, University of Vermont. There were 29 women and 3 men with a mean age of 52 years (range, 35 to 82 years). Two patients underwent repeated examinations at their physician’s request. For the purpose of the study, these were considered separate patient encounters. Based on results of physical examinations and laboratory data, patients were designated to have limited or diffuse scleroderma on the basis of current criteria.17 All patients had a physical examination for signs of pulmonary hypertension (jugular venous distention, right ventricular heave, accentuated pulmonic closure sound) by a cardiologist blinded to Doppler echocardiographic data. Patients also had 12-lead ECGs that were blindly reviewed for the presence of right atrial enlargement and right ventricular hypertrophy.18 Treatment with vasodilators was discontinued 48 h prior to the examination when deemed clinically safe (n=3). However, 18 patients were still receiving vasodilators (calcium antagonists [n=15], angiotensin-converting enzyme inhibitors [n=2], or both [n=1]) at the time of testing. Baseline clinical characteristics are presented in Table 1.

**Echocardiography**

All echocardiograms were performed by a single sonographer (R.W.B.). All studies were performed using a phased array ultrasoundoscope (Acuson XP-5; Acuson Inc; Mountain View, Calif) with a combined 2.5-MHz imaging/continuous-wave Doppler and color Doppler transducer. Doppler recordings were made from the parasternal, apical, and subcostal positions using modified views when appropriate. A systematic search was performed using two-dimensional and color-flow Doppler to identify the most complete tricuspid regurgitant jet followed by continuous-wave Doppler acquisition of spectral envelopes of the greatest maximal velocity and density. The systolic tricuspid pressure gradient was calculated using the modified Bernoulli equation:

\[ P = 4 \times v^2 \]

where v represents the maximal regurgitant velocity in meters per second.19

**Estimated Right Atrial Pressure**

Measurements of inferior vena cava diameters were made from long-axis subxiphoid views. Right atrial pressure was estimated using the caval respiratory index as described by Kircher et al.20 When the caval respiratory index exceeded 50%, the assumed right atrial pressure was 5 mm Hg. When the caval index was less than 50%, the assumed right atrial pressure was 15 mm Hg.

**Estimated Pulmonary Artery Systolic Pressure**

The estimated PA, was calculated as the sum of the tricuspid gradient and the estimated right atrial pressure. This method is highly accurate over a wide range of pulmonary pressures at our institution with an R-sq for the correlation between Doppler and catheter-measured PA, of 0.93, and a standard error of the estimate of 4.7 mm Hg.13 Pulmonary hypertension was defined as a PA, of 30 mm Hg or greater.

**Interobserver Variability**

All studies were reviewed by two independent echocardiographers blinded to all clinical and hemodynamic information. Variations were determined by calculation of a correlation coefficient with use of linear regression with a least squares method.

**Statistical Analysis**

All data management and statistical analysis tasks were performed using software (MINITAB; version 9.0) on personal computer (IBM compatible). Continuous measures are summarized as mean values±SDs, while categorical items are given as percentages. Comparisons between patients with and without pulmonary hypertension were performed using Student’s t test (all p values are two-tailed) for continuous variables and \( \chi^2 \) analysis for categorical variables. Differences were considered statistically significant if the null hypothesis could be rejected at the 5% probability level.

**Results**

Adequate images and Doppler spectral envelopes of tricuspid regurgitation were obtained in 33 of 34 examinations (97%). The calculated PA, ranged from 15 to 95 mm Hg with a mean of 30±14 mm Hg.

Twelve patients (35% of total) had pulmonary hypertension with calculated PA, between 30 and 95 mm Hg (mean±SD=43±18 mm Hg). Of these, two had PA, greater than 50 mm Hg, 1 with a value of 56 and the other 95 mm Hg.

A comparison of clinical variables in patients with measurable PA, with normal and elevated PA, is shown in Table 2. There were no statistically significant differences at baseline in patients with and without elevated PA, only 4 patients had evidence of pulmonary hypertension by physical examination alone (n=2), ECG alone (right atrial enlargement; n=1), or both (n=1). The PA, in these patients was 21, 31, 34, and 95 mm Hg, respectively.

Twenty-one patients had chest radiographs performed within 1 year of echocardiography. Seventeen were entirely normal, three had diffuse interstitial changes, and one had significant pulmonary fibrosis. Two of the four patients with radiographic abnormalities had pulmonary hypertension. Of the 17 patients with normal chest radiographs, 6 (35%) had pulmonary hypertension. Four patients with pulmonary hypertension did not have chest radiographs.

Pulmonary function testing was available in 14 pa-
tients within 1 year of echocardiography. Three had reduced diffusing capacity and evidence of airflow obstruction, two had reduced diffusing capacity and evidence of a restrictive defect, two had isolated evidence of restrictive impairment, two had isolated reductions in diffusing capacity, and one had isolated airflow obstruction. Four studies had entirely normal results. Three of the four patients with normal results of pulmonary function tests had Doppler evidence of pulmonary hypertension. Of the ten patients with abnormal results of pulmonary function tests, six did not have Doppler evidence of pulmonary hypertension.

**Table 2—Clinical Characteristics in the Setting of Normal vs Elevated PA, (n=33)*

<table>
<thead>
<tr>
<th></th>
<th>Elevated PA, No. (%) (n=12) (35%)</th>
<th>Normal PA, No. (%) (n=21) (65%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean±SD</td>
<td>56±13</td>
<td>51±11</td>
<td>NS</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>11 (92)</td>
<td>20 (95)</td>
<td>NS</td>
</tr>
<tr>
<td>Limited disease</td>
<td>11 (92)</td>
<td>17 (81)</td>
<td>NS</td>
</tr>
<tr>
<td>Diffuse disease</td>
<td>1 (8)</td>
<td>4 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco exposure</td>
<td>6 (50)</td>
<td>8 (38)</td>
<td>NS</td>
</tr>
<tr>
<td>Symptoms (PND, DOE, orthopnea)</td>
<td>9 (75)</td>
<td>13 (62)</td>
<td>NS</td>
</tr>
<tr>
<td>RAE or RVH</td>
<td>1 (8)</td>
<td>1 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>RV leak, increased P2 or JVP</td>
<td>3 (25)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Vasodilators at time of testing</td>
<td>6 (50)</td>
<td>12 (57)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*See Table 1 for explanation of abbreviations.

**DISCUSSION**

Although the sample size is not sufficiently large to comprise a true prevalence study, our results indicate that unrecognized elevation of PA is present in a significant proportion of patients with scleroderma with a prevalence rate of 35% in our cohort. Only four patients in the total cohort had evidence of pulmonary hypertension by physical examination or ECG. Further, the prevalence of pulmonary symptoms was similar in patients with (9/12; 75%) and without (13/21; 62%) elevated PA. Thus, clinical assessment did not have discriminant power with regard to presence of elevation in PA.

Pulmonary parenchymal abnormalities are recognized with increasing frequency as a complication of collagen vascular disease. In patients previously designated to have the CREST variant of scleroderma, for example, as many as 60 to 70% develop abnormal results of pulmonary function tests during the course of their disease despite a significantly lower incidence of either symptoms of dyspnea or radiographic abnormalities.4 In this setting, four major patterns of pulmonary injury have been described, including vascular changes with or without associated pulmonary hypertension, a usual interstitial pneumonia pattern of interstitial fibrosis, small airways damage, and combinations of the three.5 Of these, isolated pulmonary vascular injury is the most common histologic feature, occurring in 50% of autopsy and surgical pathologic specimens of patients with CREST syndrome.6 In contrast, CREST syndrome patients with pulmonary hypertension due to isolated vascular injury comprise only 10% of all CREST patients studied at the same institution and typically present with exertional dyspnea and accentuated pulmonic valve closure.4 A subset of these patients have isolated reductions in the diffusing capacity of carbon monoxide (Dco); survival is severely reduced in these patients.21 However, the positive predictive value of this pattern of pulmonary function testing for predicting the presence of pulmonary hypertension has not been well established. Indeed, the true incidence of pulmonary hypertension in scleroderma patients has been thought to be underestimated because of the extremely low sensitivity of routine clinical tests for making this diagnosis.5

Because of the interest in early identification of pulmonary hypertension at a potentially reversible stage, several investigators have considered the utility of noninvasive screening of patients with systemic sclerosis. Scheja et al5 studied 22 patients using Doppler techniques and identified 10 with elevated PA. Many of these patients were either symptomatic or had radiographic evidence of pulmonary fibrosis. Thus, there was already evidence of end-organ damage in a substantial proportion of their patients. Murata et al16 performed a similar study in 71 patients with systemic sclerosis and related syndromes. In this series, analyzable tricuspid regurgitant signals were recorded in only 39% of the cohort. Of this subgroup, 43% had Doppler evidence of pulmonary hypertension. At our institution, we have demonstrated a high degree of correlation with directly measured hemodynamics across a wide range of pressures. Using conventional echocardiographic techniques, we were able to estimate the PA in 28 of 30 patients and reported an R² of the correlation coefficient of 0.932 when compared to directly measured PA using a Swan-Ganz catheter.13 Thus, while the percentage of our patients with elevated PA is lower than that reported in some series, this is most likely due to the fact that most patients had no clinical symptoms or signs of pulmonary hyperten-
sion and by the fact that measurements were obtained in all but one subject. Further, 12 patients with normal PA, and 6 with elevated PA, were receiving vasodilators at the time of testing, which may have masked underlying pulmonary hypertension in patients with normal measured PA, and lowered the measured values in patients with elevated PA.

Treatment of patients with scleroderma and documented pulmonary hypertension has yielded mixed results. Thurm et al.22 conducted a placebo-controlled study of iloprost, a potent prostacyclin derivative and vasodilator. Ilprost infusion did not have a significant effect on pulmonary function testing, including DCO2, and failed to reverse the abnormal postural DCO2 response observed in these patients. Alpert et al.23 obtained hemodynamic measurements in ten patients with pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome, and mixed connective tissue disease who were treated with oral nifedipine. Short-term studies revealed a significant decrease in pulmonary vascular resistance (6.3±3.8 to 4.3±3.6 U; p=0.001). Similar changes were noted when 6 of the 10 patients were restudied 3 to 6 months later. More recently, Alpert et al.24 performed right heart catheterizations in eight patients with systemic sclerosis, the CREST syndrome, or mixed connective tissue disease prior to and immediately after administration of captopril.24 Half of the cohort underwent repeated right heart catheterization after 3 to 6 months of captopril therapy. At the time of both the short- and long-term studies, oral captopril therapy produced a significant decrease in mean pulmonary vascular resistance that was accompanied by a significant increase in cardiac output. Thus, while the results of directed therapy once significant pulmonary hypertension has developed have been somewhat varied, the two small hemodynamic studies at least suggest the possibility that active intervention may slow, if not reverse, the progression of this process. Early detection of preclinical pulmonary hypertension may allow for more rigorous intervention trials to better characterize hemodynamic effects as well as address the more relevant issues of mortality and quality of life. Moreover, cardiac ultrasound, when carefully performed, represents a readily available, highly accurate, and completely non-invasive means to establish a baseline pulmonary artery systolic pressure and allows for serial examinations as other trials are designed.

Limitations

Our total cohort was small but represents a relatively comprehensive sampling of patients followed up at our institution. Despite the small sample size, Doppler assessments of PA were possible in 97% of patients. We cannot exclude the possibility of type II error as an explanation for the apparent failure of non-Doppler clinical parameters to predict elevated PA. Additionally, radiographic and pulmonary function test results were not available in all patients. In those patients with complete data available, there did not appear to be any systematic differences between patients with and without pulmonary hypertension. However, we cannot exclude the possibility of an association between some measurable factor(s) and the presence of pulmonary hypertension, although this was not an a priori hypothesis of the present study.

Conclusions

In the present investigation, pulmonary hypertension was detected in 35% of patients with scleroderma in the absence of previously diagnosed pulmonary hypertension. Symptoms consistent with pulmonary hypertension had no discriminant power with regard to differentiating those with or without elevated PA. Doppler assessment of PA was possible in all but one patient. As Simonson et al.14 point out, until there is a proven effective therapy for pulmonary hypertension and the long-term clinical significance of this degree of pulmonary hypertension in asymptomatic patients is clarified, it is not possible to recommend routine screening of all patients with scleroderma at this time. However, by performing longitudinal evaluation of these patients, it will be possible to determine (1) whether pulmonary hypertension is progressive in these patients and (2) whether early therapeutic interventions can alter the natural history of the disease.

References

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