Scleroderma Patients with Combined Pulmonary Hypertension and Interstitial Lung Disease

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ABSTRACT. ***Objective.*** Most studies differentiate scleroderma associated pulmonary hypertension and interstitial lung disease (ILD) as 2 separate pathological processes, concentrating on one or the other; however, many patients have both conditions. We studied the demographics, clinical features, and prognosis of individuals with both vascular and interstitial lung disease.

Methods. A retrospective cross-sectional study of 619 patients with scleroderma who had echocardiograph and pulmonary function testing performed within 6 months of one another. Echocardiography determined the presence of pulmonary hypertension, and pulmonary function testing documented restrictive ventilatory defect (RVD) as a marker of ILD.

Results. Among the study group, 139 (22.5%) patients had isolated RVD; 119 (19.2%) isolated pulmonary hypertension; and 112 (18.1%) patients had combined RVD and pulmonary hypertension. The individuals with combined RVD and pulmonary hypertension resembled patients with isolated RVD in that they had a high prevalence of diffuse skin involvement and antitopoisomerase positivity, but they were older at diagnosis and at disease onset ($p < 0.01$). Among those with mild RVD, 39.2% had pulmonary hypertension compared to those with severe RVD, in whom 51.4% had pulmonary hypertension. Compared to those without pulmonary disease, the mortality risk ratio for patients with isolated pulmonary hypertension, combined RVD and pulmonary hypertension, and isolated RVD was 2.9, 2.4, and 1.61, respectively.

Conclusion. Patients with combined scleroderma lung disease features are more likely to have diffuse disease, represent older patients, and have a prognosis similar to individuals with isolated pulmonary hypertension, and may represent a distinct subpopulation of scleroderma. (J Rheumatol 2003;30:2398–405)

Key Indexing Terms:
SCLERODERMA PULMONARY HYPERTENSION INTERSTITIAL LUNG DISEASE

Scleroderma is a multisystem autoimmune disease with life-threatening pulmonary complications. These pulmonary complications, including interstitial lung disease (ILD) and pulmonary hypertension, are the most common causes of death in scleroderma now that renal crises are treatable with angiotensin-converting enzyme inhibitors[1]. ILD begins as inflammatory alveolitis that, if untreated, leads to fibrosis manifesting as a restrictive ventilatory defect (RVD). RVD on pulmonary function testing has been shown to be a good marker of ILD[2-4]. In nonrandomized case series, treatment of alveolitis with cyclophosphamide appears to stabilize pulmonary function tests and improve survival[5]. Pulmonary hypertension is a vasculopathy involving small and medium size arteries. Vasodilator therapy such as intravenous epoprostenol (prostacyclin) improves symptoms, exercise tolerance, and hemodynamics among scleroderma patients with pulmonary hypertension. Isolated pulmonary hypertension occurs predominantly in patients with limited scleroderma, whereas RVD occurs mostly in patients with diffuse disease[6]. While interstitial and vascular disease appear to be independent pathological processes in scleroderma, there are patients who develop both processes[7]. In general, studies have not included patients with both RVD and pulmonary hypertension, instead focusing on one or the other. Therefore, little is known about clinical features, pathologic differences, or prognosis of scleroderma patients with combined RVD and pulmonary hypertension. To study these individuals, we conducted a comprehensive review of patients seen at the Johns Hopkins and University of Maryland Scleroderma Center to determine the prevalence, clinical characteristics, and prognosis of patients with combined RVD and pulmonary hypertension.

MATERIALS AND METHODS

Patient selection. All scleroderma patients seen at least once at the Scleroderma Center between January 1, 1990, and August 31, 2001, were eligible. Charts were abstracted using a structured data collection form that documented patient demographics, family history, clinical symptoms, environmental exposures, and physical findings, American College of

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Rheumatology (ACR) criteria were assessed and patients were classified by skin involvement. Limited skin involvement was defined as skin tightening distal to elbows and knees with or without facial involvement; and diffuse skin involvement as tightening proximal to these joints or truncal involvement. Laboratory data included autoantibodies, standard blood tests, pulmonary function tests, and echocardiograms performed as routine screening tests and in accord with clinical indications. All patients met either the ACR criteria or 3/5 CREST [calcinosis, Raynaud's phenomenon (RP), esophageal dysmotility, sclerodactyly, telangiectasias] criteria for scleroderma to be included.

Pulmonary hypertension was defined by Doppler echocardiographic evidence of elevated right heart pressure. RVD was defined using pulmonary function tests. For the purpose of this study, pulmonary function tests and echocardiograms performed within 6 months of one another were considered contemporaneous. For patients who had multiple tests performed, we used the most recent echocardiogram and pulmonary function test (PFT). Because bronchoalveolar lavage, biopsies, and high resolution computer tomography (CT) scanning were performed only in patients with more severe disease, we chose to use PFT, as a screening test as a marker of ILD. PFT were standard of care and were consistent for method and indication throughout the study period. Patients were categorized into those with no pulmonary disease, with isolated RVD, with isolated pulmonary hypertension, and with combined RVD and pulmonary hypertension. For patients not seen in the clinic within the last 18 months, vital status was checked using the Social Security Death Index.

Pulmonary function testing. Percentage of predicted results for all PFT was standardized using published normal prediction equations based on sex, age, and height[8-10]. PFT included spirometry, helium lung volumes, and diffusing capacity of carbon monoxide (DLCO). Absence of RVD was defined as total lung capacity (TLC) = 80% of predicted; mild restriction, 65–79% of predicted; moderate restriction, 50–64%; and severe restriction, < 50% of predicted. Normal gas transfer defect was defined as DLCO > 70% of predicted; mild defect, 60–70%; moderate defect, 41–59%; and severe defect 40% of predicted[11].

Echocardiography. We extracted data from all echocardiograms using a standardized data form. If right ventricular systolic pressure (RVSP) or pulmonary artery pressure (PAP) was estimated, the information was organized into categories of pulmonary hypertension (RVSP = PAP). Different laboratories use somewhat different techniques to estimate right atrial pressure, which when added to the gradient across the tricuspid valve is equivalent to RVSP. Pressure ≤ 35 mm Hg indicated no pulmonary hypertension; 36–45 mm Hg, mild pulmonary hypertension; 46–55 mm Hg, moderate pulmonary hypertension; and > 55 mm Hg equaled severe pulmonary hypertension. For patients with no RVSP or PAP measurement because of the absence of identifiable tricuspid regurgitation, the pulmonary hypertension category was considered "no pulmonary hypertension" if right heart chamber enlargement, interventricular septum motion abnormality, and tricuspid valve abnormality were absent. If no information regarding the right heart was reported, the echocardiogram was not included. Echocardiograms were considered normal if the left ventricular ejection fraction was > 50% and there was no chamber enlargement, no interventricular septum motion abnormality, no pericardial effusion, and no evidence of pulmonary hypertension.

Statistical analyses. For the purpose of comparing types of lung disease, isolated RVD was defined as those with abnormal lung volumes (TLC < 80% of predicted) and no pulmonary hypertension. Isolated pulmonary hypertension was defined as those with evidence of pulmonary hypertension on echocardiography and no RVD, and combined pulmonary disease had both RVD and pulmonary hypertension. Significance testing for continuous variables used Student's t test and linear regression. Significance testing for proportions used z-statistic for dichotomous variables and chi-square test for categorical variables. Survival analysis utilized Kaplan-Meier survival methods and Cox proportional hazard modeling, with date of scleroderma diagnosis as the initial observation. The statistical significance of survival curves for different categories of lung disease was calculated using log-rank testing. Continuous variables were summarized as mean ± standard deviation, and proportions as percentages. Statistical significance was defined as a p value < 0.05. All data analysis was conducted on Stata 6.0 (Stata Corp., College Station, TX, USA).

RESULTS

From January 1, 1990, to August 31, 2001, the Scleroderma Center evaluated 1136 patients with scleroderma. We analyzed data from 619 patients (54.5% of the total group) who met inclusion criteria and had contemporaneous echocardiograms and PFT. Compared to those who were not included in the study at the time of analysis, those in the study were more likely to be current smokers, but otherwise both groups were similar in age, sex, and racial distribution (Table 1). Among the study patients, 101 were seen only once at the clinic; the remainder were followed a mean of 3.44 ± 3.2 years. Over 80% were female and the mean age was 50.5 ± 13.1 years at time of first visit (Table 1). The majority of patients were Caucasian (75.4%) and half were never smokers (49.6%). Thirty-two patients (5.2%) had a family history of autoimmune disease, 20 of whom had a family history of scleroderma. About 4% had risk factors for RVC including exposures to asbestos, radiation, dusts, or metals, while 2.6% had risk factors for pulmonary hypertension, specifically exposure to anorectic medications or a history of pulmonary emboli.

Over 73.8% met ACR criteria, and 41% had diffuse skin disease. Compared to those not in the study, study patients were statistically more likely to have diffuse disease. RP was the most common symptom in the study, more than 95% of the patients having RP at time of presentation (Table 2). We could not analyze therapeutic methods because of insufficient numbers of patients using many of the treatment options and the changing modalities over the span of the study.

Pulmonary function testing. Of the patients in the study, 59.5% had no evidence of RVD — 23.1% had mild, 11.5% moderate, and 6.0% severe restriction. Of those with RVD (n = 251), 62.2% had evidence of ILD by clinical examination (e.g., crackles), and 42% had a lung biopsy or radiologic study (chest radiograph or high resolution CT scan) that confirmed a diagnosis of ILD; not all patients had lung biopsies or radiologic studies performed. Of the patients with RVD, 6.6% had myopathy by clinical examination, muscle enzymes, electromyography, or muscle biopsy at the time of the PFT, which may in part explain their RVD. Gas transfer (DLCO) was normal in 21.5%; mild gas transfer defect was present in 14.2%, moderate in 34.7%, and severe in 29.6% of study patients.

Echocardiography. Overall, 229 of the 619 patients had normal echocardiograms, and 159 had abnormal echocardiograms but no evidence of pulmonary hypertension (e.g., decreased left ventricular ejection fraction). Thirty-seven

Table 1. Study patients seen at the Scleroderma Center over 11 years who had pulmonary function tests and echocardiograms performed within 6 months of each other compared to those in the cohort who were not included in the study.

Characteristic	Study patients, n = 619	Patients not in Study, n = 517	p
Female, %	82.9	83.2	0.89
Age, yrs	50.5 (13.1)	50.8 (14.3)	0.66
Race, %			
Caucasian	75.4	73.8	0.54
African-American	18.9	19.4	0.84
Smoking, %			
Never	49.6	46.2	0.26
Former	35.2	33.5	0.54
Current	15.2	20.4	0.02
Disease subtype, %			
Limited (distal to elbows and knees)	59.0	66.6	
Diffuse (diffuse skin involvement)	41.0	33.5	0.01
ACR criteria met?	73.8	68.9	0.06
Age of disease, yrs			
Age at scleroderma diagnosis	46.8 (13.5)	47.3 (14.5)	0.55
Age at first non-Raynaud's symptom	44.0 (13.9)	44.5 (15.1)	0.55
Age at Raynaud's onset	42.0 (14.2) years	41.2 (15.5) years	0.37
Serum antibodies*, %			
Antinuclear	86.9	84.0	0.22
Anticentromere	21.2	21.5	0.93
Antitopoisomerase	14.1	11.0	0.16

* Serologic data were available for only n = 937 (82%) of the patients overall.

Table 2. Disease manifestations and associations of patients (n = 619) at time of presentation to the Scleroderma Center.

Disease Characteristic	%
Raynaud's phenomenon	95.3
Digital pits	24.1
Active digital ulcers	13.4
Digital gangrene	2.6
Missing toes or fingers	10.5
Upper GI symptoms (heartburn, reflux, dysphagia)	75.1
Lower GI symptoms (malabsorption, pseudobstruction, obstipation)	23.1
Cardiac involvement (arrhythmia or congestive heart failure)	10.3
Elevated creatinine or history of renal crisis	9.0
Myopathy (weakness on clinical exam, EMG/biopsy consistent with myopathy)	15.0
Arthritis (tendon friction rubs, arthralgias, synovitis)	31.8
Telangiectasias	59.8
Calcinosis	11.5
Sicca symptoms (dry eyes or mouth)	38.0
Thyroid disease	14.5

(6.0%) had pericardial effusion as the only abnormality. By echocardiogram, 231 (37.3%) had evidence of pulmonary hypertension. In 6 patients (1%) there was evidence of pulmonary hypertension (right side chamber enlargement and interventricular septal deviation), yet no measurement of RVSP could be made because of the absence of identifiable tricuspid regurgitation. Mild to moderate pulmonary hypertension was found in 154 patients (24.9%), and severe pulmonary hypertension in 77 patients (12.4%). Of the 36.3% with an elevated RVSP measurement, the mean RVSP was 53.3 ± 16.4 mm Hg.

Combined RVD and pulmonary hypertension. We found 112 individuals among the 619 study patients who had both RVD by PFT and pulmonary hypertension by echocardiogram; 249 had no identifiable pulmonary disease, 139 had isolated RVD, and 119 had isolated pulmonary hypertension. The clinical characteristics of these groups are shown in Table 3. There were no sex differences between those with no pulmonary disease, with isolated RVD, with isolated pulmonary hypertension, and with combined RVD and pulmonary hypertension. Because many individuals had multiple sets of PFT and echocardiograms that were contemporaneous, we also analyzed the first set, and found similar results to those presented.

Individuals with combined RVD and pulmonary hypertension clinically resembled patients with isolated RVD, but differed in that they were 7.4 years older at diagnosis and 7.3–8 years older at disease onset. The prevalence and severity of pulmonary hypertension increases as the severity of RVD increases (Figure 1). Among those with mild RVD, 39.2% had some degree of pulmonary hypertension compared to those with severe RVD, among whom 51.6% had some degree of pulmonary hypertension. Patients with combined RVD and pulmonary hypertension had the same

Table 3. Comparison of characteristics between patients with no pulmonary disease, isolated pulmonary hypertension (PHTN), isolated restrictive ventilatory defect (RVD), and combined RVD and PHTN.

	Neither, n = 249	Isolated PHTN, n = 119	Isolated RVD, n = 139	Combined RVD and PHTN, n = 112
Female, %	87.6	80.7	75.5	83.9
Age, yrs				
At diagnosis	46.3 (13.0)*	49.2 (12.5)	42.8 (13.2)*	50.2 (14.6)
At first non-Raynaud's symptom	43.2 (13.1)*	46.4 (14.1)	40.0 (12.5)*	48.0 (15.3)
At Raynaud's onset	41.4 (13.7)*	42.6 (13.9)	39.1 (13.7)*	46.4 (15.2)
Race, %				
Caucasian	85.5*	81.5*	57.6	68.8
African-American	10.4*	11.8*	32.4	28.6
Disease subtype, %				
Limited	65.9	69.7	45.3	49.1
Diffuse	34.1	30.3	54.7	50.9
ACR criteria	64.3	75.6	84.9	79.5
Serum antibodies, %				
Anticentromere	28.7*	29.2*	8.8	10.9
Antitopoisomerase	7.9*	11.5	26.3	16.3
Pulmonary function tests, (% of predicted)				
FEV1	87.3 ± 17.5*	82.6 ± 21.5*	64.7 ± 16.6	64.4 ± 15.8
FVC	89.5 ± 16.6*	82.7 ± 20.4*	62.5 ± 14.8	61.6 ± 14.2
TLC	92.3 ± 10.7*	96.0 ± 11.9*	65.6 ± 11.8	63.0 ± 11.9
VC	91.9 ± 14.7*	89.2 ± 15.4*	61.7 ± 15.2	61.3 ± 15.0
RV	102.3 ± 24.9*	109.7 ± 41.6*	75.6 ± 23.4*	67.9 ± 19.4
DLCO	62.8 ± 15.6*	47.9 ± 20.2*	41.9 ± 14.4*	37.6 ± 15.1
Echocardiography				
RVSP	28 ± 5*	53 ± 17	29 ± 4*	54 ± 16

* Statistically significant difference compared to patients in the combined category. FEV: forced expiratory volume; FVC: forced vital capacity; TLC: total lung capacity; VC: vital capacity; RV: residual volume; DLCO: diffusing capacity of carbon monoxide.

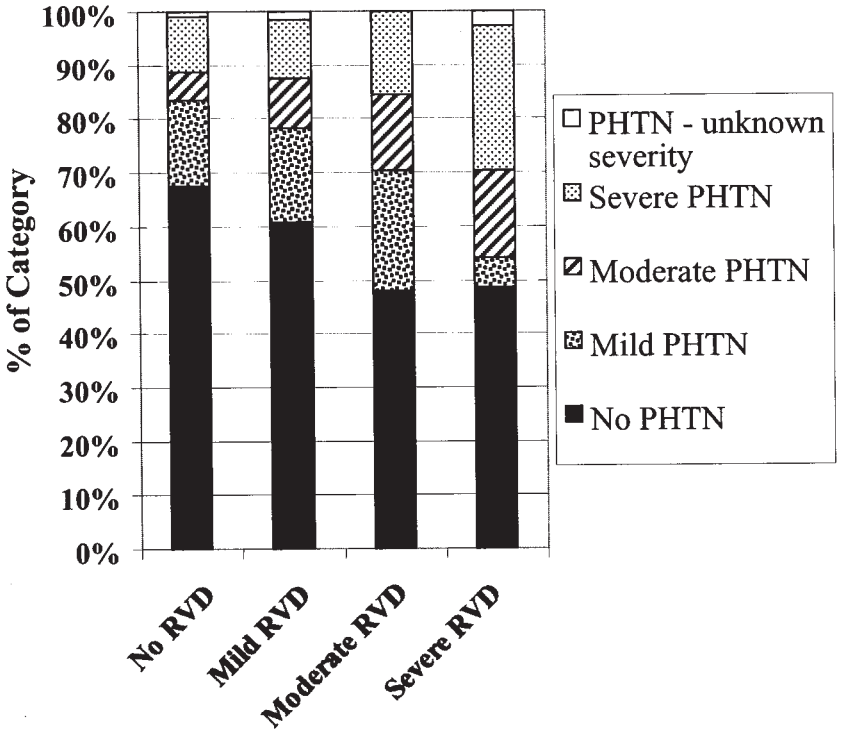

Figure 1. Restriction by pulmonary function test and pulmonary hypertension (PHTN) by echocardiography in patients who had an assessment of PHTN made by the echocardiographer. Patients who did not have an RVSP estimate but a normal right heart were included among those with no PHTN. Patients with evidence of PHTN, but with no RVSP estimate because of absence of tricuspid regurgitation, are categorized as PHTN – unknown severity.

degree of restriction as patients with isolated RVD, and the same severity of pulmonary hypertension as those with the isolated pulmonary hypertension (Figures 2 and 3).

Cox proportional hazard analysis revealed that patients with combined RVD and pulmonary hypertension had a hazard of death 2.40 times higher than those who had no pulmonary disease; 2.07 times higher after adjusting for age, sex, and race (Table 4). Utilizing date of onset of RP or date of first non-RP symptom rather than the date of diagnosis as a reference date yielded similar results. Pulmonary disease of any kind was associated with increased risk of death (Figure 4). The Kaplan-Meier curves show that the probability of survival for patients with combined RVD and pulmonary hypertension is similar to those with isolated pulmonary hypertension ($p = 0.62$), but patients with either isolated pulmonary hypertension or combined RVD and pulmonary hypertension had statistically worse survival than those with no pulmonary disease ($p < 0.01$ and $p = 0.01$, respectively). When we examined only those seen repeatedly at the Scleroderma Center and who met ACR criteria (a subgroup more likely to have severe scleroderma), then the survival of those with combined disease was still significantly worse ($p = 0.05$).

DISCUSSION

This study provides the first description of patients with combined restrictive ventilatory defect and pulmonary hypertension. In demographics, extent of skin disease, and lung function, they resemble those with isolated RVD. However, they have pulmonary hypertension as severe as those with isolated pulmonary hypertension and were just as likely to die as those with isolated pulmonary hypertension, 2.40 times greater than those with no pulmonary disease.

Our patient population was similar to previous series of scleroderma patients[12-14]. Our overall prevalence of pulmonary hypertension (37.3% of 619 patients) was similar to previous series by Ungerer, *et al*[15] (33% of patients) and Battle, *et al*[16] (35% of 34 patients). Our overall prevalence of RVD (40.5% of 619 patients) confirms and extends the findings of Peters-Golden, *et al*[17] (45% of 69 patients). In examining forced vital capacity, Steen, *et al* found 40.3% of patients had forced vital capacities < 75% of predicted, suggestive of restrictive ventilatory disease[18]. Because we utilized total lung capacity rather than forced vital capacity, these results cannot be directly compared, but they do suggest a similar prevalence of RVD. Survival in patients with isolated pulmonary hypertension in this study was similar to other studies; however, the survival of patients with isolated RVD was better[4,19]. The difference in isolated RVD survival may be related to our definition of isolated RVD; we included mild pulmonary function changes in the abnormal category and we separated those with combined RVD and pulmonary hypertension into a separate category with poorer prognosis. Although it

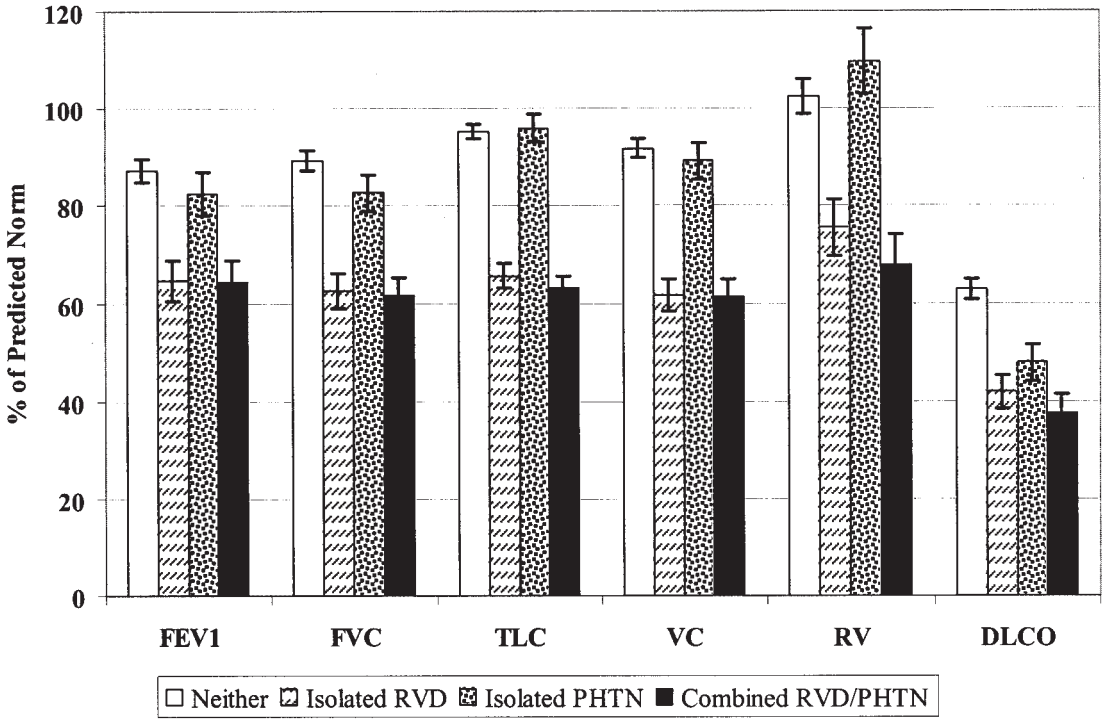

Figure 2. Comparison of percentage of predicted lung volumes and DLCO between those with no pulmonary disease, with isolated restriction, with isolated pulmonary hypertension (PHTN), and with combined restrictive ventilatory defect (RVD) and PHTN disorder (bars indicate the mean; 95% CI of SEM indicated by line).

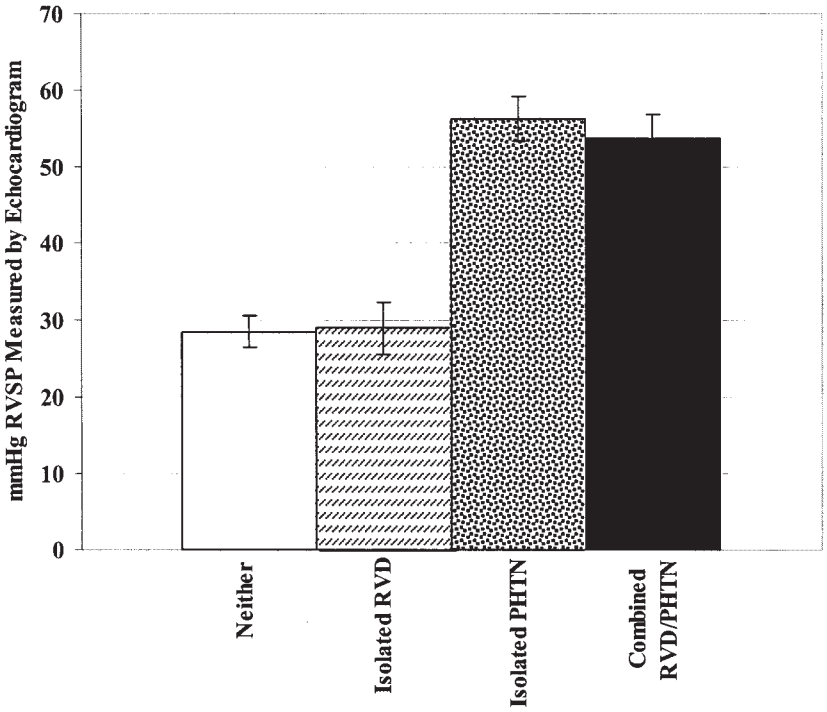

Figure 3. Comparison of right ventricular systolic pressure (RVSP) measured by Doppler echocardiography between those with no pulmonary disease, with isolated restrictive ventilatory defect (RVD), with isolated pulmonary hypertension (PHTN), and with combined RVD and PHTN (bars indicate the mean; 95% CI of SEM indicated by line).

Table 4. Cox proportional hazard ratio of risk of death by pulmonary disease categorization, where patients with no pulmonary disease are the reference group. The adjusted model adjusts for age, sex, and race.

	Hazard Ratio	p	Adjusted Hazard Ratio	p
No pulmonary disorder	1.0	—	1.0	—
Isolated RVD	1.61	0.24	1.29	0.55
Isolated PHTN	2.90	< 0.01	2.40	0.02
Combined RVD and PHTN	2.40	0.01	2.07	0.04

includes alveolitis, RVD does not equate to active lung inflammation or alveolitis, which has a known poor prognosis[6]. This made the isolated RVD category appear to have a much better than expected prognosis.

This study has several limitations. The patients were limited to those referred to a subspecialty center, and therefore possibly biased toward more severe cases — diffuse disease or more severe symptoms. However, comparisons with other studies indicate that our population is representative of scleroderma seen elsewhere. Only 54.5% of the patients seen at the Scleroderma Center were available for the study because not all echocardiograms and PFT were performed contemporaneously and therefore were not included. In addition, many echocardiograms failed to assess the right heart and the presence of pulmonary hypertension. Although right heart catheterization is the gold standard, echocardiography has been shown to be a good test for pulmonary hypertension[20]. Physicians influenced by patients reporting symptoms or a decline in functional status may have been more likely to order contemporaneous echocardiograms and PFT. We chose to use RVD instead of radiologic or biopsy proven ILD, which may have included patients with other causes of RVD (e.g., diaphragmatic myopathy). While high resolution CT scans may be more sensitive and lung biopsy would be more specific for interstitial disease, such studies were not routinely done in those with mild or stable pulmonary function abnormalities. Because patients with limited disease may have delayed diagnosis, use of the date of diagnosis as the reference point for survival analysis may bias the survival of these patients toward poorer prognosis[21]; however, our results using different reference dates gave similar hazard ratios.

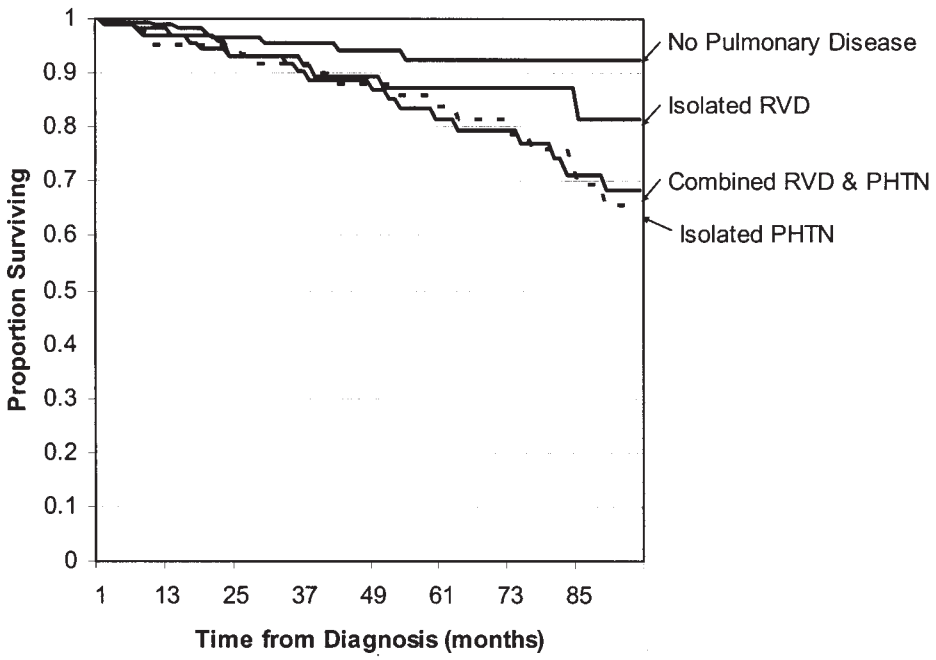

Figure 4. Kaplan-Meier survival graph comparing those with no pulmonary disease, with isolated restrictive ventilatory defect (RVD), with isolated pulmonary hypertension (PHTN), and with combined RVD and PHTN, where time is represented in months since the diagnosis of scleroderma. The graph for "no pulmonary disease" was not statistically different from that for "isolated RVD"; however, it was statistically different from that for "isolated PHTN" ($p < 0.01$) and for "combined RVD and PHTN" ($p = 0.01$).

We were concerned that the high mortality of patients with combined lung disease may be the result of endstage ILD causing pulmonary hypertension. However, we were unable to find any reports on endstage scleroderma ILD and the degree of pulmonary hypertension. We did find that individuals awaiting lung transplant for idiopathic pulmonary fibrosis had a mean RVSP of 57 ± 23 mm Hg, similar to our findings[22]. Individuals with interstitial disease from idiopathic pulmonary fibrosis compared to isolated scleroderma interstitial disease are older at disease onset, have shorter disease duration, and have a much worse prognosis[23]. Pathologically, collagen vascular diseases are usually in a different classification — a more cellular process and a better prognosis[24]. Because scleroderma combined lung disease has not been well studied, and other lung diseases are clinically and pathologically dissimilar, comparisons are difficult.

Because patients with combined RVD and pulmonary hypertension are often excluded from therapy trials, it is unknown how best to treat them. Early intervention may benefit these individuals, such as early referral for lung transplant. In patients with combined RVD and pulmonary hypertension, pulmonary vasodilator therapy may be complicated by worsening hypoxemia due to increased perfusion and ventilation mismatch[25]. Therefore, patients with combined RVD and pulmonary hypertension have difficulty using the major medication for treatment of pulmonary hypertension. And with further characterization of patients with combined RVD and pulmonary hypertension, these patients may be included in trials of new therapies as they become available. Hopefully, future studies will examine which pulmonary complication develops first, pulmonary hypertension or RVD.

In summary, the scleroderma population with combined restrictive ventilatory defect and pulmonary hypertension make up a substantial proportion of scleroderma patients. Clinically they resemble patients with isolated restrictive ventilatory defect, but they have mortality similar to those with isolated pulmonary hypertension. This is just the beginning of improved understanding of this subpopulation; more work is needed in the areas of pathologic differences, natural history, and therapy response differences.

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