Hemodynamics and Survival in Patients With Pulmonary Arterial Hypertension Related to Systemic Sclerosis*

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Study objectives: The goal of this study was to determine whether the survival of patients with pulmonary hypertension related to systemic sclerosis (SScPH) was different from that of patients with other forms of pulmonary arterial hypertension.

Design: Retrospective cohort study.

Setting: Tertiary care medical center.

Patients: Our cohort was composed of 33 patients with pulmonary hypertension that is sporadic, familial, or related to anorexigen use (PPH) and 22 patients with SScPH who underwent initial pulmonary artery catheterization and vasodilator study at our center between January 1997 and June 2001.

Measurements and results: Patients with SScPH had somewhat lower percentage of predicted lung volumes than patients with PPH (total lung capacity, 80% vs 92%; p = 0.06) and had lower percentage of predicted diffusion capacity of the lung for carbon monoxide (42% vs 68%; p = 0.0002). Right atrial pressure, pulmonary artery pressure, and cardiac index were similar between the groups. Patients with SScPH and PPH were treated with usual medical therapies, such as digoxin, warfarin, and continuous IV epoprostenol. Despite these similarities, the risk of death in patients with SScPH was higher than in patients with PPH (unadjusted hazard ratio, 2.9; 95% confidence interval, 1.1 to 7.8; p = 0.03). This increased risk appeared to persist after adjustment for a variety of demographic, hemodynamic, or treatment variables.

Conclusions: Despite having similar hemodynamics, patients with SScPH have a higher risk of death than patients with PPH. Future studies of the mechanism and therapy of pulmonary arterial hypertension should focus on the distinctions between the different forms of this disease.

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Key words: calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia syndrome; cohort studies; pulmonary hypertension; systemic sclerosis; survival analysis

Abbreviations: CI = confidence interval; DLCO = diffusion capacity of the lung for carbon monoxide; DLCO% = percentage of predicted diffusion capacity of the lung for carbon monoxide; FVC% = percentage of predicted FVC; HR = hazard ratio; PAWP = mean pulmonary artery pressure; PPH = pulmonary hypertension that is sporadic, familial, or related to anorexigen use; PVR = pulmonary vascular resistance; SSc = systemic sclerosis; SScPH = pulmonary hypertension related to systemic sclerosis; TLC = total lung capacity; TLC% = percentage of predicted total lung capacity
in the small pulmonary arteries.\textsuperscript{4–7} The hemodynamic profile of patients with SScPH is similar to that of patients with PPH, \textit{i.e.}, pulmonary vascular resistance (PVR) is high and cardiac output is often low.\textsuperscript{5,9} In addition, patients with SScPH and PPH show hemodynamic and functional improvements after initiation of treatment with epoprostenol.\textsuperscript{10–13}

Patients with pulmonary hypertension related to anorexigen use have a survival rate that is similar to that of patients with sporadic or familial pulmonary hypertension.\textsuperscript{14} However, it is not known whether the survival of patients with SScPH is different from that of patients with PPH. The only published cohort study comparing patients with SScPH and PPH resulted from the National Institutes of Health National Registry on Primary Pulmonary Hypertension, initiated in 1981.\textsuperscript{8} Patients with collagen vascular disease appeared to have a higher risk of death than patients with PPH, although this result was not statistically significant. There were a small number of patients with systemic sclerosis (SSc) included, and this study was performed before the use of continuous IV epoprostenol. Therefore, limited conclusions may be drawn from the Registry regarding the outcomes of SScPH patients under current diagnostic and therapeutic strategies.

Although more recent studies have also suggested worse outcomes in patients with pulmonary hypertension related to connective tissue diseases,\textsuperscript{15} none have specifically studied a cohort of patients with SScPH in comparison to patients with other forms of pulmonary arterial hypertension. It would be important for future investigations of mechanism and therapy to determine if outcomes in patients with SScPH were distinct from that of patients with other forms of pulmonary arterial hypertension. Our primary aim was to determine whether patients with SScPH have a higher mortality than patients with PPH after initial pulmonary artery catheterization and vasodilator study.

**Study Patients**

**Inclusion Criteria:** Inclusion criteria were as follows: (1) a mean pulmonary artery pressure (PAm) > 25 mm Hg at rest or PAm > 30 mm Hg with exercise; (2) PPH or SScPH; (3) absence of significant restrictive lung disease (FVC or total lung capacity [TLC] > 60% of predicted); (4) initial pulmonary artery catheterization and vasodilator study performed at our medical center between January 1997 and July 2001.

**Exclusion Criteria:** Exclusion criteria were as follows: (1) elevated pulmonary artery occlusion pressure or left-ventricular end-diastolic pressure and/or evidence of left-sided cardiac disease; (2) congenital heart disease; (3) significant obstructive lung disease (FEV\textsubscript{1}/FVC ratio < 0.72 and FEV\textsubscript{1} < 50% of predicted); (4) sleep apnea requiring nocturnal ventilation; (5) other etiology of pulmonary hypertension; and (6) previous pulmonary artery catheterization and vasodilator study.

**Data Collection**

Data were collected from the outpatient, inpatient, and cardiac catheterization records. The primary outcome variable was all-cause mortality. A secondary outcome was cardiovascular death.\textsuperscript{16} One patient underwent lung transplantation and was considered to have reached a cardiovascular end point at the time of transplantation.

We assessed outcomes through chart review and computerized search of the National Death Index. A patient was considered to be alive at the last medical contact noted in the chart if it was within 3 months of the completion of the study period. For patients who were not seen in the previous 3 months, patients or their primary care physicians were contacted by telephone.

Pulmonary artery catheterization was performed either in the Cardiac Catheterization Laboratory or at the bedside. After pulmonary artery catheterization, short-acting vasodilators such as nitric oxide and epoprostenol were administered to patients to test vasoreactivity. Patients who had a decrease in PVR by \( \geq 20\% \) were considered to have an acute response to vasodilators.

**Statistical Analysis**

Continuous variables were summarized by the mean \( \pm \) SD. Categorical variables were summarized by frequencies with 95\% confidence intervals (CIs). Bivariate analyses were performed comparing patients with PPH to patients with SScPH. We compared continuous variables using Student's t tests for normally distributed variables and Wilcoxon rank-sum tests for nonnormally distributed variables. Dichotomous variables were compared using \( \chi^2 \) tests or Fisher exact tests, when appropriate.

We assessed transplant-free survival from initial pulmonary artery catheterization using the Kaplan-Meier estimator. The log-rank test was used to compare the time to event between patients with PPH and patients with SScPH. Bivariate and multivariate survival analyses were performed using Cox proportional hazards methods.\textsuperscript{17} We constructed models with diagnosis and potential confounding variables that were thought to be clinically important or were found on bivariate analysis to be associated with the diagnosis or outcome with \( p \) values \( < 0.20 \). Covariates that reduced the unadjusted hazard ratio (HR) of diagnosis by \( > 10\% \) were considered to be confounders. Individual models were constructed for diagnosis and each covariate.

The proportional hazards assumption was examined for diagnosis and all covariates using Schoenfeld residuals and tests based on weighted residuals.\textsuperscript{18} Covariates that failed to meet this assumption were included as time-dependent variables.

Bivariate analyses were performed with available data. We
performed simple imputation for missing data points for analysis in the multivariable models; p values < 0.05 were considered statistically significant.

Results

Patient Population

Our cohort was composed of 33 patients with PPH and 22 patients with SScPH. Of patients with PPH, 22 patients (67%) had sporadic pulmonary hypertension, 3 patients (9%) had familial pulmonary hypertension, and 8 patients (24%) had pulmonary hypertension related to anorexigen use. Of patients with SScPH, 16 patients (73%) had SSc with limited cutaneous scleroderma, 4 patients (18%) had SSc with diffuse cutaneous scleroderma, and 2 patients (9%) had SSc in overlap. Patients with missing data were not significantly different from those with complete data sets in terms of age, gender, diagnosis, hemodynamics, or survival (p > 0.15, data not shown). There were no patients who were unavailable for follow-up.

Bivariate and Multivariate Analyses

Baseline demographics were similar in patients with PPH and patients with SScPH (Table 1). There was no significant difference in the time from diagnosis of pulmonary hypertension to pulmonary artery catheterization. There were no significant differences in right atrial pressure, PAm, cardiac index, PVR, or acute response to vasodilators between patients with PPH and patients with SScPH.

Patients with SScPH had lower values for percent-age of predicted FVC (FVC%) and percentage of predicted TLC (TLC%) than patients with PPH, although these differences were not statistically significant (Table 2). Patients with SScPH had a lower percentage of predicted diffusion capacity of the lung for carbon monoxide (DLCO%) [corrected for hemoglobin] than patients with PPH. A diagnosis of SScPH was associated with a lower DLCO% than a diagnosis of PPH, even after adjustment for TLC% and FVC% (data not shown, p = 0.001). Patients with SSc with limited scleroderma had a mean FVC% that was similar to that of patients with SSc with diffuse scleroderma (77% vs 74%, respectively; p = 0.79). The mean oxygen saturation was 0.96 ± 0.04 in patients with SScPH (n = 21) and 0.95 ± 0.04 in patients with PPH (n = 31) [p = 0.23] at the initial right-heart catheterization. These results may have been spuriously similar due to differences in the use of supplemental oxygen.

Patients with SScPH had a significantly lower mean hemoglobin concentration than patients with PPH (SScPH, 13.1 ± 1.9 g/dL vs PPH, 14.1 ± 2.2 g/dL; p = 0.04) at pulmonary artery catheterization. There were no significant differences in the mean values of creatinine or BUN.

Patients received similar therapies during the study period (Table 3). Fifty-four percent of patients with SScPH and 61% of patients with PPH were treated with continuous IV epoprostenol immediately after the initial pulmonary artery catheteriza-

<table>
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<tr>
<th>Table 1—Demographic and Hemodynamic Characteristics by Diagnosis*</th>
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<tr>
<td>Characteristics</td>
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<tr>
<td>Female sex, %</td>
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<tr>
<td>White race, %</td>
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<tr>
<td>Age, yr</td>
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<tr>
<td>Median time from diagnosis of pulmonary hypertension, yr</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
</tr>
<tr>
<td>PAS, mm Hg</td>
</tr>
<tr>
<td>PAD, mm Hg</td>
</tr>
<tr>
<td>PAm, mm Hg</td>
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<tr>
<td>PAOP, mm Hg</td>
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<tr>
<td>Cardiac index, L/min/m²</td>
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<tr>
<td>PVR, dynes/cm²</td>
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<td>Acute vasoreactivity, No. (%)</td>
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*Data are presented as mean ± SD unless otherwise indicated; FAS = pulmonary artery systolic pressure; PAD = pulmonary artery diastolic pressure; PAOP = pulmonary artery occlusion pressure.

<table>
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<th>Table 2—Pulmonary Function Test Results by Diagnosis*</th>
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<tr>
<td>Variables</td>
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<tr>
<td>FVC%</td>
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<tr>
<td>FEV₁%</td>
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<tr>
<td>TLC%</td>
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<tr>
<td>DLCO%</td>
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*Data are expressed as mean ± SD. FEV₁% = percentage of predicted FEV₁.

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<tr>
<th>Table 3—Medical Treatment Variables by Diagnosis*</th>
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<tr>
<td>Variables</td>
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<tr>
<td>Calcium-channel blockers</td>
</tr>
<tr>
<td>Epoprostenol treatment initiated at catheterization</td>
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<tr>
<td>Epoprostenol treatment ever</td>
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<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
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<tr>
<td>Digoxin</td>
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<tr>
<td>Warfarin</td>
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*Data are presented as No. (%).
tion (p = 0.65). The majority of patients from both groups were treated with warfarin (SScPH, 73%; PPH, 82%; p = 0.51).

Despite the similarities in hemodynamics and treatments in the groups, there were significant differences in outcomes. Patients with SScPH had a significantly shorter survival time after initial pulmonary artery catheterization than patients with PPH (log-rank test, χ² = 4.88, p = 0.03) [Fig 1]. The 1-year survival estimates were 55% (95% CI, 26 to 76%) for patients with SScPH and 84% (95% CI, 66 to 93%) for patients with PPH.

The unadjusted risk of death during the study period for patients with SScPH compared to patients with PPH was 2.9 (95% CI, 1.1 to 7.8; p = 0.03) [Table 4]. This risk (or HR) decreased after adjustment for right atrial pressure, but did not change after adjustment for PAm, cardiac index, PVR, or acute vasodilator response.

Digoxin and epoprostenol use partially confounded the association between diagnosis and outcome, as the HRs of SScPH vs PPH were reduced after adjustment for these factors. Although the point estimates of all HRs were consistent with an increased risk of death in patients with SScPH, some p values were not <0.05.

Parameters such as lung volumes and diffusion capacity of the lung for carbon monoxide (DLco), which are affected in SSc, should not be analyzed as potential confounders, as these variables may be part of the causal pathway between the disease process of SSc and worse outcomes.19 With this caveat, we include these adjusted results for completeness. The HRs for SScPH vs PPH when adjusted for FVC% or TLC% were not significantly changed. The HR of death for patients with SScPH vs PPH after adjustment for DLco% was 1.7 (95% CI, 0.5 to 5.0; p = 0.36). After adjustment for serum creatinine and hemoglobin, the relative risk of death was 2.5 (95% CI, 0.92 to 6.8; p = 0.07) and 3.0 (95% CI, 1.1 to 8.2; p = 0.04), respectively.

There were five cardiovascular deaths in each group (23% of patients with SScPH and 15% of patients with PPH). Cardiovascular causes of death accounted for 55% of the deaths in SScPH and 50% of the deaths in PPH. The cause of death of three patients could not be classified. These patients were censored at their date of death for the analysis of the cardiovascular end point. The HR of reaching a cardiovascular end point for SScPH vs PPH was 3.1 (95% CI, 0.72 to 13.0; p = 0.13).

**Table 4—HRs for Death for Patients With SScPH and PPH Adjusted for Covariates**

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR for SScPH vs PPH</th>
<th>95% CI</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>2.9</td>
<td>1.1–7.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted for:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>2.5</td>
<td>0.92–6.7</td>
<td>0.07</td>
</tr>
<tr>
<td>PAm</td>
<td>2.9</td>
<td>1.1–7.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>3.2</td>
<td>1.2–8.6</td>
<td>0.02</td>
</tr>
<tr>
<td>PVR</td>
<td>3.3</td>
<td>1.2–9.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>2.8</td>
<td>1.0–7.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Warfarin</td>
<td>3.2</td>
<td>1.2–8.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2.6</td>
<td>0.97–6.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>2.5</td>
<td>0.90–6.7</td>
<td>0.07</td>
</tr>
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</table>

![Figure 1](image-url)  
**Figure 1.** Kaplan-Meier survival estimates of patients with SScPH and PPH.
DISCUSSION

We did not observe significant differences in demographics or hemodynamics between patients with SScPH and patients with PPH. The somewhat lower mean FVC% and TLC% in patients with SScPH are likely due to mild parenchymal lung disease, which may accompany SScPH. Of note, pulmonary function testing revealed mild restriction in many of our patients with PPH as well, which has been documented previously. These differences have unclear clinical relevance.

We found a significantly lower DLCO% in patients with SScPH than in patients with PPH despite adjustment for lung volumes. It is possible that more pronounced pulmonary vascular intimal or medial hypertrophy may cause more severe ventilation/perfusion mismatch or result in decreased pulmonary blood volume in patients with SScPH as compared with other patients with pulmonary arterial hypertension. Alternatively, more pronounced capillary or parenchymal fibrosis, not reflected in the other pulmonary function tests, may account for this difference. In either case, the impairment in DLCO could mediate the increased risk of death in patients with SScPH, as discussed below.

We found a prevalence of vasoreactivity in patients with SScPH similar to that found in other published series using similar criteria to define a significant response to acute vasodilators. Lower estimates have been published; however, certain of these studies have included patients with a variety of connective tissue diseases. We (and others) have found that despite a relatively high rate of vasoreactivity with acute vasodilator testing, patients with SSc rarely (if ever) show clinical improvement with calcium-channel blockers (personal communication; Robyn Barst, MD, Elizabeth Klings, MD, Ivan Robbins, MD; April 2002). This implies that the traditional parameters thought to represent an improved outcome and response to therapy derived from the experience with PPH may not necessarily apply to other forms of pulmonary arterial hypertension.

The survival of patients with SScPH in our cohort was similar to that of other studies in this population, although small sample size prevented precise estimates. Studies that have reported better long-term survival in patients with SScPH have different inclusion criteria and may have included a healthier patient population.

There was a higher risk of death for patients with SScPH than for patients with PPH in our cohort. We found that different patterns of epoprostenol and digoxin use partially confounded the association between diagnosis and outcome. Patients with SSc were somewhat less likely to initially receive epoprostenol, which was associated with improved outcome. In our practice, it has been observed that some patients with SSc may have very limited dexterity due to sclerodactyly, thereby limiting the ability to be self-sufficient in the maintenance of a continuous epoprostenol infusion. This may have limited the initial use of continuous IV epoprostenol in certain patients with SSc. Digoxin was also a confounder in the multivariable model; the use of this medication in certain patients may simply be a marker of worse clinical cardiovascular function.

Our results suggested that there is an increased risk of cardiovascular death in patients with SScPH vs PPH, although wide CIs limit the definitiveness of this finding. Future studies should be designed and powered to answer this question conclusively.

Possible Sources of the Increased Risk of Mortality in SScPH vs PPH

This study does not definitively identify the causes of increased mortality in patients with SScPH. Lung volumes, spirometric values, and DLCO are clearly affected in patients with SSc, and these factors may increase vulnerability to cardiopulmonary insults, such as pneumonia. Patients with SSc commonly have esophageal dysfunction, and this may result in an increased risk of aspiration. These factors could account for the higher risk of death in patients with SScPH than in patients with PPH.

It is possible that patients with SScPH have more severe vascular disease than patients with PPH. The reduced DLCO even after adjustment for lung volumes supports this hypothesis. However, the reduced DLCO may reflect subclinical parenchymal lung disease that is not detected by other measures.

Cardiac involvement in SSc is common. Myocardial fibrosis may be detrimental to right ventricular systolic or diastolic function in the setting of pulmonary vascular disease, resulting in an increased risk of death. Investigators have found that 100% of patients with SSc have coronary perfusion abnormalities on single-photon emission CT thallium imaging. It is thought that the site of increased resistance is arteriolar (or distal) and vasospastic in nature. Coronary vascular insufficiency may lead to ischemia and explain the increased risk in patients with SScPH.

Potential Limitations of this Study

There are no clinical or laboratory criteria that reliably differentiate between SScPH and pulmonary hypertension due to hypoxemia or interstitial lung disease secondary to SSc. Clinical studies have used a variety of spirometric values and radiographic findings to differentiate the primary vascular process.
from parenchymal disease. In our study, the inclusion of SSc patients with pulmonary hypertension due to interstitial lung disease is unlikely because (1) we used the same definition of restrictive lung disease for both patients with SScPH and patients with PPH, and (2) it has been suggested that resting pulmonary hypertension (which was present in all patients with SScPH in our cohort) is not usually present unless the vital capacity is < 50% of predicted in interstitial lung disease.

Lead-time bias could be present if patients with SScPH were referred or evaluated with pulmonary artery catheterization at a later time point in their disease process than patients with PPH. Substantial bias is unlikely, however, as patients with SSc usually receive care from a primary care physician and a rheumatologist, increasing their chances for medical contacts. Patients with PPH often have no other medical problems, and diagnosis is frequently delayed. The World Health Organization recommendations for yearly screening echocardiography and heightened awareness in the rheumatologic community of SScPH would likely result in earlier detection of pulmonary hypertension in this disease than in PPH. If true, our findings may underestimate the actualrisk associated with SScPH compared to PPH.

Misclassification bias is not a concern for the primary end point, all-cause mortality. We used multiple different strategies to assess each patient’s status at the conclusion of the follow-up period, resulting in a 0% loss to follow-up.

Factors for which we have not accounted, such as functional status or exercise capacity, may confound the association of disease type and outcomes. Unfortunately, these data were not available for the patients in our cohort.

Our sample size was not large enough to permit multivariable analysis with simultaneous adjustment for multiple confounders. Also, small sample size limited the precision of the estimated HRs.

**Conclusion**

Our results suggest that patients with SScPH have a risk of death that is greater than that of patients with PPH after initial evaluation for vasodilator therapy. Although we have not defined the physiologic factor that mediates this increased risk, it is likely that the fibrotic process affects cardiac and/or pulmonary vascular function in patients with SSc.

The worse outcomes in this patient group may have implications in future clinical trials, as this subgroup may not respond to medical interventions tested in patients with other forms of pulmonary arterial hypertension. A priori subgroup comparisons should be planned to specifically examine the effects of therapy on patients with SScPH. Future efforts should focus on confirming our results and elucidating the mechanisms that contribute to the increased risk of death in patients with SScPH compared with PPH.

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