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Changes in Estimated Right Ventricular Systolic Pressure Predict Mortality and Pulmonary Hypertension in a Cohort of Scleroderma Patients

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Abstract

Objectives—Annual echocardiography screening is widely used in scleroderma, but the utility of longitudinal assessment is unknown. Accordingly, we evaluated whether change in right ventricular systolic pressure (RVSP) was a risk factor for mortality and development of pulmonary arterial hypertension (PAH) in a cohort of scleroderma patients.

Methods—The study population consisted of scleroderma patients who had at least 3 echocardiograms and pulmonary function tests (PFTs) over 1 year as part of routine care. The annual rate of change in RVSP was determined for each subject. Cox proportional hazards regression was performed to assess the association between PAH and mortality, and change in RVSP/year, adjusted for relevant covariates.

Results—613 scleroderma patients with 3244 echocardiograms were studied. The adjusted relative hazards of PAH and mortality were 1.08 (95% CI 1.05,1.11) and 1.12 (95% CI 1.08,1.15) per 1mmHg increase in RVSP/year, respectively. Compared to patients with a stable RVSP, the relative hazards for development of PAH was 1.90 (95% CI 0.91,3.96), 5.09 (95% CI 2.53,10.26) and 6.15 (95% CI 3.58,10.56) for subjects whose RVSP increased at rates of 1–1.99, 2–2.99 and 3+mmHg/year. Compared to the same reference group, the relative hazards for death was 0.92

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(95% CI 0.48,1.73), 2.16 (95% CI 1.16,4.01), and 5.05 (95% CI 3.47,7.34) for subjects whose RVSP increased at rates of 1–1.99, 2–2.99, and 3+mmHg/year.

Conclusions—In a population of scleroderma patients, the rate of increase in RVSP is a risk factor for mortality and PAH even after adjustment for clinical characteristics and longitudinal PFT data.

Keywords

Systemic Sclerosis; Pulmonary Hypertension; Echocardiography

INTRODUCTION

Patients with systemic sclerosis (scleroderma) are a population at high risk to develop cardiopulmonary disease with pulmonary arterial hypertension (PAH). It is known that PAH is a leading cause of mortality and morbidity among these patients and may occur alone or in conjunction with interstitial lung disease and/or cardiac dysfunction. Despite the availability of therapeutic agents, PAH continues to exact a heavy toll on the long-term survival of patients with scleroderma. Once PAH is present in a scleroderma patient, the prognosis is poor. After diagnosis of PAH, the 3-year mortality rate was 44% in two investigations. [1, 2]

A goal in managing patients is early detection of PAH in order to establish prognosis and institute early treatment. As a result, annual echocardiography screening is recommended for patients with scleroderma despite data that suggest that right ventricular systolic pressure (RVSP) on echocardiography has only a moderately positive correlation with both mean pulmonary artery pressure and invasively determined tricuspid gradient. [3] It has also been suggested that RVSP elevation is not a risk factor for the future development of PAH in scleroderma, [4] but most of the supporting data for this conclusion was from studies that defined pulmonary hypertension by echocardiography rather than right heart catheterization. [5, 6] We hypothesized that the rate of change in RVSP on serial echocardiograms would be a risk factor for development of clinical PAH and death in patients with scleroderma. Accordingly, we analyzed the relationship between serial changes in echocardiography and subsequent development of clinical PAH and survival in a cohort of well-characterized patients with scleroderma.

METHODS

Subjects were identified through the Johns Hopkins Scleroderma Center database, which was established in 1990 and approved by Johns Hopkins Institutional Review Board. All data have been recorded prospectively at the first visit and longitudinally at 6-month intervals. All clinically ordered echocardiograms, pulmonary function tests (PFTs), and right heart catheterization (RHC) data are entered into the database. Each subject in the database fulfills either American College of Rheumatology criteria for scleroderma, [7] meets at least 3 of 5 CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) criteria, or has definite Raynaud's phenomenon, abnormal nailfold capillaries, and a scleroderma-specific autoantibody. This investigation included all subjects who had 3 echocardiograms with a recorded measurable estimated RVSP and 3 PFTs over at least 1 year. A minimum requirement of 3 data points for echocardiograms and PFTs was chosen to ensure there was enough data to examine longitudinal trends; the effects of examining only 2 data points were later examined in sensitivity analyses. Because patients with an acute decompensation event may have more frequent echocardiograms or PFTs during a short interval, we required that data had to span over at least 1 year. Data on the

date of scleroderma onset as defined by the first non-Raynaud's symptom also must have been recorded to be included. All data through April 2010 were analyzed.

Demographic data, disease onset date, disease characteristics, smoking history, autoantibody status, and outcome measures including mortality status were abstracted from the database. Vital status was verified by use of the Social Security Death Index. Scleroderma subtype was defined by established criteria. [8] Echocardiograms and PFTs were performed at various sites as part of routine clinical care, and all measurements of forced vital capacity (FVC) and diffusing capacity (DLCO) were standardized by gender and age. [9, 10] As these data were acquired over 2 decades and uniform criteria were not utilized to refer patients for RHC during this time, RHC was performed in patients based on the clinical judgment of the treating physician. RHC-confirmed PAH was defined by a mean pulmonary artery pressure (MPAP) ≥ 25 mmHg and a pulmonary capillary wedge pressure (PCWP) <15 mmHg. Pulmonary venous hypertension (PVH) was defined by a MPAP ≥ 25 mmHg and a PCWP ≥ 15 mmHg. Pulmonary hypertension (PH) was defined by a MPAP ≥ 25 mmHg.

Statistical analysis

Statistical analyses were done using SAS 9.2 software (SAS Institute, Cary, NC). Clinical and demographic data were compared between our included study population and the overall Scleroderma Center cohort to ensure that included subjects were representative of our patient base. Differences in continuous and dichotomous or categorical variables were assessed by the Student's t-test and chi-square test.

Annual rates of change in RVSP (RVSP), FVC (FVC), and DLCO (DLCO) were determined by performing linear regression of RVSP, FVC, and DLCO on years from first non-Raynaud's symptom for each subject. The validity of the linearity assumption was tested and confirmed through regression diagnostics. Simple Cox proportional hazards regression analyses were performed to assess the bivariate associations between PAH and

RVSP, and between PAH and other scleroderma characteristics. Multivariable Cox proportional hazards regression analysis was then performed to assess the association between PAH and RVSP, adjusted for baseline RVSP, FVC, DLCO, age at scleroderma onset, race, gender, scleroderma subtype, and smoking history. These variables were fixed in all analyses because of their clinical relevance. Autoantibody status was examined in bivariate analysis and included in multivariable models if statistically significantly associated with our outcomes of interest ($p < 0.05$). Similar Cox proportional hazards regression analysis was performed with mortality as the outcome, and the multivariable model included RHC-confirmed PAH as a potential confounder in the association between

RVSP and mortality. Subjects without the outcome of interest were administratively censored at date of last visit. The validity of the proportional hazards assumption was confirmed by examining Schoenfeld residuals and assessing their association with time. For all survival analyses, the timescale was defined as time from the 1st non-Raynaud's symptom in years.

The RVSP was also examined as a categorical variable and compared to the reference group that had a RVSP <1 mmHg/year. RVSP rate categories included increases of 1–1.99, 2–2.99, and 3+ mmHg/year. To identify the minimum relevant RVSP, Cox proportional hazards models were performed to examine the association between our outcomes, the development of PAH and mortality, and the RVSP as a categorical variable. In addition, a log-rank test for trend was performed to explore a “dose-response” relationship between the RVSP rate categories and survival times. Kaplan-Meier survival plots were examined to demonstrate the relationship between our two outcomes and RVSP, and log-rank tests were performed to identify the threshold RVSP cutoff at which survival was statistically significantly different for the population.

Multiple sensitivity analyses were also performed to examine the effects of different inclusion criteria, time origin, and missing data (Supplement 1).

RESULTS

Out of 2519 scleroderma patients in the database, 1077 had adequate data on the timing of the clinical onset of scleroderma and had 3 echocardiograms over at least one year. Among these 1077, 613 patients had 3 echocardiograms with an estimated RVSP and 3 PFTs over a time period of 1 year. Therefore, our final study population consisted of 613 scleroderma patients with 3244 echocardiograms.

Our study population's mean age at scleroderma onset was 45.2 years (SD 13.1) (Table 1). The majority of patients were Caucasian, women and had limited scleroderma. Our study sample had more women (86.6% vs. 82.1%, $p<0.01$) and fewer smokers (44.1% vs. 49.8%, $p<0.01$) compared to the remainder of our scleroderma population that did not meet study entry criteria. The study sample was otherwise comparable on key clinical characteristics. Subjects who did not meet the inclusion criteria of having 3+ echocardiograms and PFTs over 1 year had less follow-up time at our Center (2.1 years vs. 7.7 years, $p<0.01$) as expected.

The mean baseline FVC, DLCO, and RVSP were 78.3% predicted, 74.6% predicted and 35.2 mmHg, respectively. Of the 157 patients who had a RHC as part of their routine clinical care, 114 had RHC-confirmed PH: 83 (13.5%) with PAH and 31 (5.1%) with PVH. By the end of follow-up, 143 patients (23.3%) were deceased. The median disease duration at last follow-up or death was 11.3 years (mean 13.3; SD 8.3). The mean RVSP for the whole study population was 1.50 mmHg/year (SD 4.7).

Adjusted Relationship between PAH and Δ RVSP

The relative hazards of PAH was 1.08 (95% CI 1.05,1.11) per 1mmHg increase in RVSP/year, adjusted for the other covariates in the model (Table 2). Higher baseline RVSP and older age at scleroderma onset were also associated with increased risk of PAH, but declining FVC and DLCO, gender, race, scleroderma subtype, and smoking history were not. Autoantibody status was not included in the multivariable model; none of the 3 autoantibodies under study were associated with PAH risk in bivariate analysis (data not shown).

Adjusted Relationship between Mortality and Δ RVSP

The relative hazards of death was 1.12 (95% CI 1.08,1.15) per 1mmHg increase in RVSP/year, after adjustment for the other covariates in the model (Table 2). Higher baseline RVSP, RHC-confirmed PAH, decline in FVC, decline in DLCO, and older age at scleroderma onset were also statistically significantly associated with increased risk of mortality. Anti-centromere positivity was protective. Race, gender, scleroderma subtype, and smoking status were not associated with mortality.

Identification of the minimum rate of change in RVSP/year that impacts development of PAH and mortality on a population level

Compared to patients whose RVSP was stable over time (Δ RVSP<1mmHg/year), the relative hazards for development of PAH was 1.90 (95% CI 0.91,3.96), 5.09 (95% CI 2.53,10.26) and 6.15 (95% CI 3.58,10.56) for subjects whose RVSP increased at rates of 1–1.99, 2–2.99 and 3+ mmHg/year (Table 3). Kaplan-Meier survival curves demonstrate that patients with a Δ RVSP $\geq$ 2 mmHg/year have a significantly shorter median time to developing PAH compared to patients with a Δ RVSP <2 mmHg/year (Figure 1; 22.7 vs.

36.5 years, $p < 0.0001$). Compared to the same reference group, the relative hazards for death was 0.92 (95% CI 0.48, 1.73), 2.16 (95% CI 1.16, 4.01), and 5.05 (95% CI 3.47, 7.34) for subjects whose RVSP increased at rates of 1–1.99, 2–2.99, and 3+ mmHg/year, respectively. Even after adjustment for RHC-confirmed PAH, the relative hazards for death remained significantly higher among patients whose RVSP increased at 2–2.99 mmHg/year (HR 2.05; 95% CI 1.09, 3.86) and 3+ mmHg/year (HR 4.81; 95% CI 3.24, 7.15). A log-rank test for trend showed evidence of a “dose-response” relationship between survival times and RVSP categories ($p < 0.0001$). Kaplan-Meier survival curves demonstrate that patients with an increase in RVSP ≥ 2 mmHg/year have a significantly shorter survival than subjects with a change in RVSP < 2 mmHg/year (Figure 2; median 17.5 vs. 42.7 years, $p < 0.0001$).

DISCUSSION

Although widely used in scleroderma, a single measure of echocardiographic RVSP has limited value in establishing the risk for development of PAH and subsequent mortality. We hypothesized that important prognostic information could be obtained by measuring the rate of change of RVSP on serial echocardiograms. Accordingly, we analyzed whether change in RVSP on serial echocardiograms is a risk factor for mortality and the development of PAH in a large cohort of well-characterized scleroderma patients. After adjusting for other clinically relevant covariates, including change in FVC and DLCO, we found that a RVSP ≥ 2 mmHg/year predicts risk of PAH development and death in the overall cohort. In addition, an increasing RVSP was predictive of mortality even after adjusting for the presence of known PAH. These data strongly suggest that, when considering a population of scleroderma patients, longitudinal echocardiography data contributes meaningful information about risk for PAH and mortality beyond that available from clinical characteristics and PFT data. It is important to note that the threshold rates of change in RVSP identified in this study are based on population-level data and cannot be used to determine an individual patient's risk of developing PAH. Identification of the threshold rate of change in RVSP that should prompt RHC in an individual patient will require prospective investigation.

Although echocardiography is a recommended screening test for PH, its limited sensitivity and only moderate correlation with invasively determined PA systolic pressure are notable limitations. [11, 12] In addition, the short-term variability of RVSP measurements is unknown; thus, in an individual patient, RVSP elevation requires confirmation with RHC. Despite these shortcomings, echocardiography has been found to have a high specificity for PH in scleroderma and may provide prognostic information about mortality. In a study of 49 scleroderma patients with clinically suspected PH, Hsu and colleagues examined three noninvasive screening tools (PFT, echocardiogram, and PA diameter on cardiac MRI) and compared their test characteristics with invasive assessment of PH by RHC. [11] Echocardiography was the most useful screening test given its high specificity, positive predictive value and area under receiver-operating characteristic curve. As our study has demonstrated, baseline RVSP on initial echocardiography is also predictive of mortality. A recent investigation demonstrated that 1, 2, and 3 year survival was significantly less in patients who had an initial RVSP ≥ 36 mmHg compared to those with an RVSP < 36 mmHg. [13] A prior study detected a trend toward increased mortality in scleroderma patients with a rising PA systolic pressure on echocardiogram compared to patients who had static or falling PA systolic pressures, but this study was underpowered with only 152 scleroderma subjects and was based solely on echocardiogram data. [14] In addition, the relationship between changes in RVSP and development of PAH was not examined, likely because RHC was not routinely used at that time. Our population study suggests that increasing RVSP may identify high-risk subgroups that need to be followed closely for development of PAH and mortality. Although there is no proven treatment that can prevent the development of PAH

in patients with scleroderma, identification of high risk patient subsets could inform clinical trial development, leading to treatments that can prevent or delay this complication. Our data also demonstrate that increasing RVSP is a risk factor for mortality even after adjustment for the presence of RHC-confirmed PAH, suggesting that change in RVSP over time may also be an independent marker of cardiac dysfunction.

Our practice is to perform echocardiography and pulmonary function tests annually. Patients with an isolated low DLCO, [6, 15] a tricuspid regurgitant velocity $>3\text{m/s}$ or $2.5\text{--}3\text{ m/s}$ with unexplained dyspnea, [16] or an increasing RVSP warrant consideration for invasive hemodynamic assessment. It is important to note that our study is based on a large population trend and therefore the specific threshold or rate of change in RVSP that should prompt RHC for an individual patient remains unknown. There is increasing interest in the development of algorithms to identify patients at high risk for PAH who should undergo RHC. [17, 18] In addition to modeling baseline FVC and DLCO, FVC, DLCO, autoantibody status, brain natriuretic peptide (BNP) levels, oxygen saturation, WHO classification, and baseline RVSP, RVSP should be examined as a covariate. It is likely that the threshold RVSP that is clinically relevant in an individual patient is higher than our population-level estimates because of limited precision in estimating RVSP on echocardiography. Prospective investigations are necessary to develop meaningful algorithms for early detection of PAH, to interrogate whether use of these algorithms improves survival, and to examine the risks, benefits, and cost-effectiveness of these screening tools.

Our investigation was conducted in a large, observational cohort at a tertiary referral center. In addition, we selected for subjects who had serial echocardiograms with a recorded estimated RVSP, and therefore these patients may have come to our center with greater frequency or more severe disease. Although these features may bias our sample to having a higher rate of PAH, the clinical characteristics of our study sample were generally representative of our Center's patient population with the exception of gender and smoking status. Our study sample had more women and fewer smokers, findings that may bias our estimates towards the null given the increased mortality risk in men with scleroderma and in smokers. A potential limitation of our study design is that echocardiograms were performed and interpreted at many sites by different operators with varying levels of expertise. The strength of this approach is that it reflects routine clinical practice and suggests that these results are generalizable to the overall scleroderma community. However, RVSP estimates were not available for all echocardiogram studies. When we performed a sensitivity analysis imputing a baseline RVSP for patients with no baseline RVSP estimate and no evidence of RV dilation, our findings were unchanged. Another limitation is that the rates of change over time in RVSP, FVC, and DLCO were estimated as linear regression coefficients. Although regression diagnostics demonstrated that the linearity assumption was valid, the estimated rate of change in RVSP may have been calculated with a wide range of echocardiogram studies (i.e. range 3–17 echocardiograms/person). This could introduce measurement error in our primary covariate, rate of change in RVSP. To address this, we examined a standardized rate of change in RVSP (Supplement 1) in our multivariable Cox models, and this yielded similar results. Patients had to survive to enter into our study, and this may bias our findings towards the null. Our study may have misclassified subjects as not having PAH as not all subjects had RHC. Additionally, all-cause mortality was assessed, as cause of death was not known in all subjects. The effect of vasodilator therapy on mortality was not examined since we do not capture data on whether vasodilators are prescribed for severe Raynaud's phenomenon versus PAH. Unfortunately, we were not able to examine BNP levels, an important biomarker of PH, as this data was not systematically obtained.

This large, observational study demonstrated that an increasing RVSP is a risk factor for development of PAH and mortality in scleroderma even after adjustment for clinical characteristics and longitudinal PFT data. The estimated RVSP by echocardiography is not a precise measure of true PA pressure and therefore RHC is needed to diagnose PAH. Although the thresholds identified cannot be used for clinical decision making in an individual patient, our data demonstrate that a rising estimated RVSP identifies a subset of patients at risk to develop PAH and mortality and supports the recommendation of periodic testing. Physician education about the importance of echocardiography assessment in patients with scleroderma is necessary since it is not routinely performed in community-based rheumatology practices. [19] Ultimately, we feel that a composite of information including clinical status, PFTs, biomarkers (e.g. pro BNP, serology) and serial echocardiography will best identify patients at risk for PAH and increased mortality. PAH is a life-threatening complication that is treatable, and early detection and intervention will likely improve morbidity and survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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No. at Risk

RVSP < 2mmHG/yr	435	259	71	25	5
RVSP ≥ 2mmHG/yr	178	78	26	6	2

Figure 1. Shorter time to PAH in scleroderma patients with a change in RVSP ≥ 2mmHg/year compared to those with a change in RVSP < 2 mmHg/year ($p < 0.0001$).

No. at Risk

RVSP < 2mmHG/yr	435	265	73	27	6
RVSP ≥ 2mmHG/yr	178	87	26	7	2

Figure 2.

Shorter time to death in scleroderma patients with a change in RVSP ≥ 2mmHg/year compared to those with a change in RVSP < 2 mmHg/year ($p < 0.0001$).

Table 1

Comparison of Baseline Characteristics between Study Population and Excluded Cohort

Variable	Study sample (N=613)	Excluded cohort (N=1906)
Age at scleroderma onset, years, mean (SD) *	45.2 (13.1)	45.7 (14.8)
Women, no. (%) [§]	531 (86.6)	1564 (82.1)
Race, no. (%) **		
White	470 (76.9)	1446 (75.9)
African American	106 (17.3)	328 (17.2)
Asian	18 (3.0)	33 (1.7)
Other	17 (2.8)	98 (5.2)
Scleroderma classification, no. (%)		
Limited	377 (61.5)	1210 (63.5)
Diffuse	236 (38.5)	696 (36.5)
Disease duration at first visit, years, mean (SD) *	5.4 (6.9)	6.2 (7.7)
Raynaud's duration at first visit, years, mean (SD) ***	8.2 (10.1)	9.3 (11.1)
Follow-up duration at last visit or death, yrs, mean (SD) † [§]	7.7 (4.6)	2.1 (3.4)
Smoking, no. (%) †† [§]		
Never	341 (55.9)	937 (50.2)
Former	209 (34.3)	691 (37.0)
Current	60 (9.8)	240 (12.8)
Autoantibody status, ever positive, no. (%) ‡		
Centromere	143 (26.2)	353 (30.4)
Topoisomerase-I	123 (24.1)	223 (21.2)
Ribonucleoprotein (RNP)	40 (8.6)	86 (8.7)

* N=1881 for excluded cohort.

** N=611 for study population and 1905 for excluded cohort.

*** N=608 for study population and 1823 for excluded cohort.

† N=1861 for excluded cohort.

†† N=610 for study population and 1868 for excluded cohort.

‡ For anti-centromere antibodies, N=546 for study population and 1163 for excluded cohort. For anti-topoisomerase I antibodies, N=511 for study population and 1052 for excluded cohort. For anti-RNP antibodies, N=463 for study population and 984 for excluded cohort.

§ p<0.01.

Table 2

Association of Rate of Change in RVSP With Pulmonary Arterial Hypertension (PAH) and Mortality, Adjusted Relative Hazards (95% CI)

Variable	PAH*	Mortality**
Rate of increase in RVSP (mmHg/year)	1.08 (1.05,1.11)	1.12 (1.08,1.15)
Baseline RVSP (mmHg)	1.03 (1.02,1.04)	1.02 (1.01,1.03)
RHC-Confirmed PAH		1.68 (1.11,2.54)
Rate of decrease in FVC (%/year)	1.04 (0.95,1.14)	1.09 (1.01,1.17)
Rate of decrease in DLCO (%/year)	1.04 (0.98,1.11)	1.11 (1.05,1.18)
Age at Scleroderma onset (years)	1.03 (1.02,1.05)	1.05 (1.03,1.07)
Race: white vs. all others	0.66 (0.39,1.12)	0.65 (0.41,1.03)
Gender: female vs. male	1.09 (0.53,2.22)	1.20 (0.67,2.14)
Subtype: diffuse vs. limited	1.68 (1.00, 2.82)	1.48 (0.93,2.36)
Smoking: ever vs. never	0.98 (0.63,1.52)	1.50 (0.98,2.29)
Anti-centromere, ever positive		0.27 (0.15,0.49)

* N=608. Adjusted model includes rate of change in RVSP, baseline RVSP, rate of decrease in FVC, rate of decrease in DLCO, age at scleroderma onset, race, gender, subtype, and smoking status.

** N=561. Adjusted model also includes RHC-confirmed PAH and anti-centromere positivity.

RVSP: right ventricular systolic pressure, RHC: right heart catheterization, FVC: forced vital capacity, DLCO: diffusing capacity.

Table 3

Relative Hazards (95% CI) of Pulmonary Arterial Hypertension (PAH) and Mortality at Various Rates of Change in RVSP/year

Rate of change in RVSP/year	PAH	Mortality	Mortality*
< 1 mmHg/year (N=352)	Reference	Reference	Reference
1–1.99 mmHg/year (N=83)	1.90 (0.91,3.96)	0.92 (0.48,1.73)	0.88 (0.46,1.68)
2–2.99 mmHg/year (N=53)	5.09 (2.53,10.26)	2.16 (1.16,4.01)	2.05 (1.09,3.86)
3+ mmHg/year (N=125)	6.15 (3.58,10.56)	5.05 (3.47,7.34)	4.81 (3.24,7.15)

* Controlled for RHC-confirmed PAH.