Exercise Echocardiography Predicts Future Development of Pulmonary Hypertension in a High-risk Cohort of Patients with Systemic Sclerosis

Kaitlin A. Quinn, Stephanie R. Wappel, Tunay Kuru, and Virginia D. Steen

ABSTRACT. ***Objective.*** To evaluate whether a positive exercise echocardiogram (EE) predicts future development of pulmonary arterial hypertension (PAH) in a high-risk cohort of patients with systemic sclerosis (SSc).

Methods. Patients with SSc with features associated with an increased risk for PAH were recruited into a prospective, observational cohort. All patients underwent clinical assessment and EE. A positive EE was defined as an increase of ≥ 20 mmHg in the right ventricular systolic pressure with exercise. All patients with positive EE underwent right heart catheterization (RHC).

Results. The study included 85 patients. In the positive EE cohort, 10 of 43 patients (23%) developed resting pulmonary hypertension (PH) on RHC over a mean 4-year followup period [4 with PAH, 5 with pulmonary venous hypertension (PVH), and 1 with PH associated with interstitial lung disease]. In the persistently negative EE cohort, only 3 of 42 patients (7%) developed resting PH (1 PAH, 2 PVH; p = 0.04). Of the remaining 33 patients in the positive EE group who did not develop resting PH, 22 (67%) had a persistently positive EE over an average 5-year followup period.

Conclusion. In this high-risk cohort of patients with SSc, a positive EE may predict the future development of resting PH. In addition, a majority of patients may have a persistently positive EE for years without progression to resting PH. Finally, a consistently negative EE may identify patients at low risk for future PH. (First Release December 15 2019; J Rheumatol 2020;47:708–13; doi:10.3899/jrheum.190226)

Key Indexing Terms:
SYSTEMIC SCLEROSIS PULMONARY HYPERTENSION
EXERCISE ECHOCARDIOGRAPHY

Pulmonary arterial hypertension (PAH) is a leading cause of death in patients with systemic sclerosis (SSc)[1,2]. PAH is often detected late in the disease course[3], and early identification of patients with PAH is essential to initiating treatment to improve function and survival in patients with this debilitating disease[4].

Right heart catheterization (RHC) is the gold standard for the diagnosis of pulmonary hypertension (PH)[5], with World Health Organization (WHO) Group I PAH defined as a mean pulmonary artery pressure (PAP) of 25 mmHg or greater and a pulmonary artery wedge pressure (PAWP) of < 15 mmHg. Because RHC is invasive, there is much interest in finding less-invasive tests to detect PH. We previously have shown that a low DLCO and an increased percentage of predicted forced vital capacity (FVC)/percentage of predicted DLCO (FVC%/DLCO%) > 1.6 are risk factors for the development of PAH[6], but studies have also suggested that exercise echocardiogram (EE) may be a tool to predict the development of PH[7,8,9,10,11,12,13].

In 2008, we reported a cohort of 54 patients identified to be high risk for development of PAH who underwent EE as a screening tool for PAH[14]. Those with a post-exercise increase in right ventricular systolic pressure (RVSP) of > 20 mmHg underwent RHC to evaluate for PAH or exercise-induced PH. At that time, exercise-induced PH was included in the WHO diagnosis of PAH. We found that 24 patients (44%) had a positive EE, with PAH confirmed by RHC in 19% of patients at rest and 62% of patients with exercise. In addition, a positive EE correlated with a positive anticentromere antibody (ACA). However, few studies have followed a cohort of SSc patients with abnormal EE over time to determine PH outcomes.

The objective of our study was to determine whether high-risk SSc patients who had a positive baseline EE were more likely to develop resting PAH over time, compared to patients with a negative baseline EE.

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MATERIALS AND METHODS

Study population. Patients with SSc who are at increased risk for future PAH were identified from the SSc patient population at MedStar Georgetown University Hospital. All patients fulfilled the preliminary criteria for the classification of SSc[15]. Entry criteria included any of the following: dyspnea on exertion, DLCO < 60% of predicted, FVC < 60% of predicted, FVC%/DLCO% ratio > 1.6, or resting RVSP on echocardiogram > 30 mmHg but < 50 mmHg. No patient had a prior diagnosis of PH. Patients were excluded if they had known coronary artery disease, a left ventricular ejection fraction < 50%, significant diastolic dysfunction (grade 2 or higher), or an inability to walk on the treadmill. In addition, patients with a resting RVSP > 50 mmHg were considered likely to have PAH and therefore were not entered into the study.

Clinical assessment. All patients underwent standard pulmonary function tests and EE using standard Bruce protocol. The initial EE was performed as a research study and patients who had their initial EE from 2004 to 2012 were eligible for enrollment in the study. A research RHC with exercise was requested on all patients who had a positive EE. After initial EE and/or RHC, patients were followed by standard of care by their rheumatologist. Repeat exercise or resting echocardiogram and/or repeat RHC was performed only as clinically indicated. Testing for antinuclear antibodies (ANA) including ACA, anti-Scl-70, and an antinucleolar pattern on the ANA was done as available from commercial laboratories.

EE protocol and assessment. The exercise portion of EE was performed immediately after resting echocardiography, during which assessment was done of diastolic dysfunction by transmitral and transtricuspid flow patterns, tissue Doppler interrogation patterns, and pulmonary venous flow patterns. After positioning the patient, the area where the tricuspid regurgitant jet was most easily identified was noted. The patients then performed a standard Bruce protocol on a treadmill to achieve 85% of predicted maximal heart rate[14]. A repeat estimate of the RVSP was performed within 1 min of completion of exercise. Additional measurements obtained included resting and exercise heart rate, pulse, time exercised, and metabolic equivalent of tasks. The baseline estimated RVSP assumed a right atrial pressure of 0–5 mmHg and RVSP was determined from peak tricuspid regurgitant jet velocity, as per American Society of Echocardiography guidelines[16]. A positive test was defined as an increase in RVSP of at least 20 mmHg over the resting RVSP, which was used in the initial study[14]. Patients were required to have at least 1 repeat echocardiogram ≥ 1 year after initial EE to be included in the study.

RHC protocol and assessment. RHC with exercise was requested on all patients who had a resting RVSP > 40 mmHg and/or a positive exercise test result. All RHC were performed by a single operator (TK) in the cardiac catheterization laboratory[14]. A flow-directed pulmonary artery catheter was placed in the right femoral vein. As the pulmonary artery catheter was advanced, right atrial pressure and right ventricular pressure were recorded in the appropriate positions. PAP was continuously recorded, and the PAWP was recorded intermittently. Cardiac output was assessed by thermodilution (Mac-Lab System; Marquette Medical Systems). Patients with resting mean PAP < 25 mmHg and PAWP < 15 mmHg underwent exercise testing. Early in the study, patients exercised in the supine position by lifting dumbbells with both arms; after 2011, lower extremity exercise using a reclining bike was performed. Patients used weights as tolerated (2-lb, 5-lb, or 10-lb) and exercised either to exhaustion or to 85% of predicted maximum heart rate, whichever was reached first. At peak exercise, heart rate, blood pressure, oxygen saturation, and PAP were documented, and PAWP and cardiac output were re-measured. Cardiac index and pulmonary vascular resistance were then recalculated as described above. The criteria for PH on longitudinal followup was defined as mean PAP > 25 mmHg on RHC[17]. Patients whose initial RHC revealed PH were excluded from the study. Exercise-induced PAH was defined as mean PAP > 30 mmHg and PAWP < 18 mmHg at peak exercise.

Statistical analysis. Patients were categorized on the basis of positive EE and negative EE. Comparisons between the 2 groups were made using a Mann-Whitney U test for continuous variables and a chi-square test for categorical variables. Means (SD) and counts (percentages) were assessed for continuous and categorical variables, respectively. The statistical package used was GraphPad and significance was established at 0.05. A Kaplan-Meier curve was used to graphically present time to development of PH.

Ethics and informed consent. All patients consented to participate in the study. An Institutional Review Board at Georgetown University approved the research (Georgetown University Biomedical IRB Committee B #2003-363).

RESULTS

Study population. A total of 100 patients were recruited into this followup study (Figure 1), including the 54 from the original study published by Steen, *et al* in 2008[14], which was still undergoing active enrollment at the time of publication. Twelve patients were excluded because they did not have a repeat EE at least 1 year after initial EE. Table 1 describes the baseline clinical and laboratory demographic features of the remaining 88 patients. Table 2 describes their baseline cardiopulmonary measurements. Three additional patients were later excluded from the study because their initial RHC, performed shortly after initial positive EE, revealed baseline resting PH. Because the purpose of the study was to determine whether EE is useful in predicting future development of PH over time, these 3 patients were not included in the analysis.

Assessment with EE. All patients underwent initial EE with a followup EE performed ≥ 1 year after initial study, with duration between studies of 4.7 ± 2.5 years. Among the 85 patients, 31 had a positive baseline EE and 54 had a negative baseline EE. Of the 54 patients in whom initial EE was negative, 42 had a persistently negative EE on repeat testing (performed ≥ 1 year after initial study) and remained in the negative EE group. However, 12 patients with an initial negative EE developed a positive EE on repeat testing between years 1 and 8 of followup.

Assessment with RHC. All patients who had a positive EE underwent RHC per study protocol, which was performed on average 6.6 ± 4.4 months after positive EE. In addition, 18 patients with a negative EE underwent RHC. The 12 patients whose negative initial EE converted to a positive EE underwent RHC upon conversion to positive. None of those 12 patients had resting PH on their first RHC, so they were subsequently included in the "positive baseline EE" group to determine whether they developed resting PH over time. This resulted in a total of 43 patients (51%) in the positive EE group and 42 (49%) in the negative EE group (Figure 1).

Table 3 shows the clinical demographic features and cardiopulmonary variables of the 2 groups. There were no statistically significant differences between groups at baseline, including no differences among antibodies. During followup, 13 patients developed resting PH. In the positive EE cohort, 10 patients (23%) developed resting PH on RHC over a mean period of 4 years, whereas only 3 patients (7%) in the negative EE cohort developed resting PH (p = 0.04).

Evaluation of PH. As shown in Table 3, a total of 13 patients

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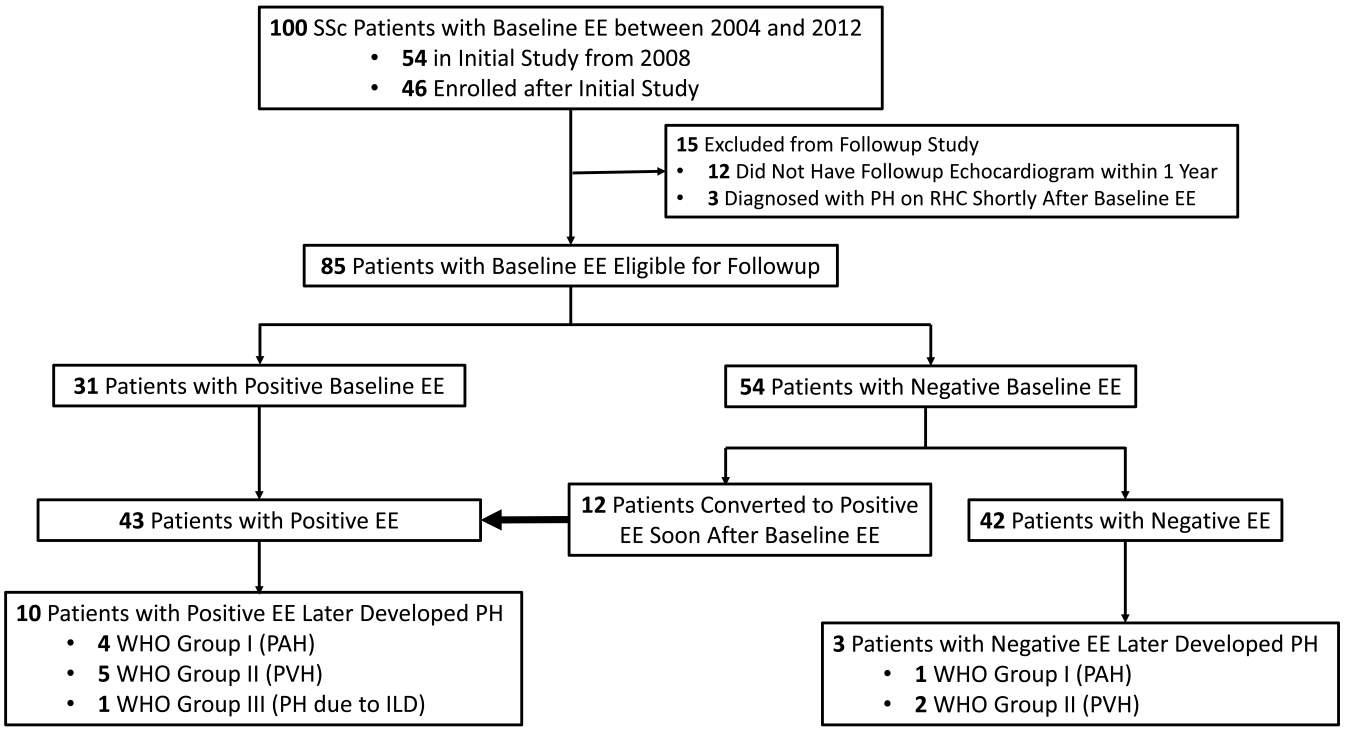

Figure 1. Flow diagram of patients who developed pulmonary hypertension (PH). One hundred patients with systemic sclerosis (SSc) underwent baseline exercise echocardiogram (EE), and 85 patients were eligible for followup evaluation; they had repeat EE ≥ 1 year after initial study, and did not have PH on initial right heart catheterization (RHC). Ten patients in the positive EE group later developed pulmonary hypertension (PH), and 3 patients with a negative baseline EE ultimately developed PH. WHO: World Health Organization; PAH: pulmonary arterial hypertension; PVH: pulmonary venous hypertension; ILD: interstitial lung disease.

Table 1. Study population baseline clinical and laboratory demographics.

Characteristics	Total, n = 88
Age, yrs ± SD	53 ± 12.5
Disease duration, yrs ± SD	7.1 ± 6.6
Race, n (%)	
White	46 (52)
African American	37 (42)
Other	5 (6)
Sex, female (%)	82 (93)
Antibodies, n (%)	
Anticentromere	26 (29)
Antinucleolar	22 (25)
Scl-70	15 (17)
U1RNP	9 (10)
RNA polymerase III	5 (6)
Unknown/other	11 (13)
SSc type, limited (%)	58 (66)

SSc: systemic sclerosis; limited: limited cutaneous SSc.

Table 2. Study population baseline cardiopulmonary measurements.

Measurement	Total, n = 88
FVC, % predicted ± SD	85.2 ± 21.0
DLCO, % predicted ± SD	63.7 ± 20.9
FVC(%)/DLCO(%) ± SD	1.4 ± 0.5
6-MWT distance, m ± SD	442 ± 103
Resting RVSP, mmHg ± SD	32 ± 7

FVC: forced vital capacity; 6-MWT: 6-minute walk test; RVSP: right ventricular systolic pressure.

developed resting PH. All 10 of the patients in the positive EE group had an initial RHC that did not show PH, then later developed PH over a median of 3.5 years (interquartile range 1.5–5 yrs). None of the 3 patients in the negative EE group who ultimately developed PH had an initial RHC, but they subsequently had a significant change in clinical symptoms that prompted further evaluation by RHC. In the 13 patients who developed PH, not all of these patients developed PAH. In the positive EE cohort, 4 patients developed PAH (WHO Group 1), 5 developed pulmonary venous hypertension (PVH; WHO Group 2), and 1 developed PH associated with interstitial lung disease (WHO Group 3). All 4 of the patients who developed PAH had exercise PAH on their initial RHC. However, 1 of the patients who developed resting PVH also had exercise PAH on the initial RHC. Two of the other 4 patients with PVH had exercise PVH during their initial RHC, and the other 2 patients had only a resting RHC performed initially. In the negative EE group, 1 patient

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Table 3. Clinical demographic features and cardiopulmonary measurements stratified by exercise echocardiogram (EE) result.

Features and Measurements	Positive EE, n = 43 (51%)	Negative EE, n = 42 (49%)	p
Age, yrs ± SD	54.7 ± 11.8	51.3 ± 13	0.27
Disease duration, yrs ± SD	7.9 ± 7.1	6.3 ± 6	0.46
Race, n (%)			0.68
White	22 (51)	24 (57)	
African American	19 (44)	15 (36)	
Antibodies, n %			0.44
Anticentromere	12 (28)	14 (33)	
Scl-70	5 (12)	9 (21)	
Antinucleolar	11 (26)	8 (19)	
SSc type, limited, %	26 (60)	30 (71)	0.28
FVC, % ± SD	84.5 ± 20	85.7 ± 22.3	0.88
DLCO, % ± SD	62.6 ± 22.3	64.7 ± 20	0.42
FVC(%)/DLCO(%) ± SD	1.5 ± 0.4	1.4 ± 0.5	0.83
Baseline 6-MWT, m ± SD	434.6 ± 103.7	450.6 ± 98.6	0.74
Baseline RVSP, mmHg ± SD	33.2 ± 7.5	31.5 ± 5.7	0.39
ΔRVSP, mm Hg ± SD	21.7 ± 7.9	10.7 ± 5.4	< 0.01
RHC mPAP*, mmHg ± SD	20.0 ± 4.9	20.4 ± 5.9	0.67
RHC PAWP*, mmHg ± SD	10.5 ± 5.4	12.3 ± 3.7	0.19
Time to followup, yrs ± SD	5 ± 2.4	4.7 ± 2.4	0.56
Developed PH, n (%)	10 (23)	3 (7)	0.04

* n = 18 for negative EE group. SSc: systemic sclerosis; limited: limited cutaneous SSc; FVC: forced vital capacity; 6-MWT: 6-minute walk test; RVSP: right ventricular systolic pressure; PH: pulmonary hypertension: RHC: right heart catheterization; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure.

developed PAH (WHO Group 1) and the other 2 patients had PVH (WHO Group 2). There were no clinical or baseline differences between the patients who developed PAH compared to those who developed PVH, including no differences in antibodies or DLCO.

Time to development of PH. Time to development of PH was stratified by EE result. Patients in the positive EE group continued to develop PH over time, whereas patients in the negative EE group developed PH early on; this then leveled off over time (p = 0.06). The Kaplan-Meier curve is shown in Figure 2.

Outcome of patients without PH. Of the remaining 33 patients in the positive EE group who did not develop resting PH, most (67%) continued to have a positive EE. This includes 18 patients who had persistent exercise-induced PH without the development of resting PH as documented on RHC over a mean of 5.3 years of followup. The EE normalized in only 5 patients (15%). Six patients (18%) did not have a repeat EE, but their resting echocardiograms remained normal (Table 4). Two patients died of other causes (stroke, infection). Among the 39 patients in the negative EE cohort who did not develop resting PH, 3 died of noncardiopulmonary problems (severe pulmonary fibrosis, infection, cancer). The others had normal resting echocardiograms (n = 36) during the 5-year followup period, and 20 had repeat EE that did not show an exercise-induced increase in RVSP.

DISCUSSION

This study evaluated the ability of EE to predict the development of resting PH over time in patients with SSc at increased risk of developing PH. The results suggest that a positive EE may predict the future development of resting PH. However, it does not necessarily predict PAH. Even in this cohort of patients with SSc at increased risk for PAH, a positive EE was also associated with resting PVH. In addition, 51% of patients with a positive baseline EE had a persistently positive EE without progression to resting PH over an average 5-year followup period. It should also be noted that 81% of the patients with a persistently positive EE had exercise PH on RHC, although they did not have resting PH.

In addition, patients with a positive EE continued to develop PH throughout the followup period. This contrasted with the negative EE group, in which several patients developed PH early on, but this leveled off over time. There was a trend toward significance with this result, but our study population was not large enough to fully evaluate this. It is unclear why those 3 patients with negative EE developed PH shortly after their baseline EE, but we do not have initial RHC data on these patients, so it is possible that this was a false-negative baseline EE. RHC was not routinely performed in followup in this group of patients unless clinically indicated, and it is also important to note that these 3 patients had a significant change in symptoms from time of negative EE to time of development of PH. Overall, most of the patients in our study with a negative baseline EE (39 of 42) did not progress to development of PH during longterm followup. This suggests that EE has a useful role in clinical practice in identifying patients with SSc who are at increased risk of PH.

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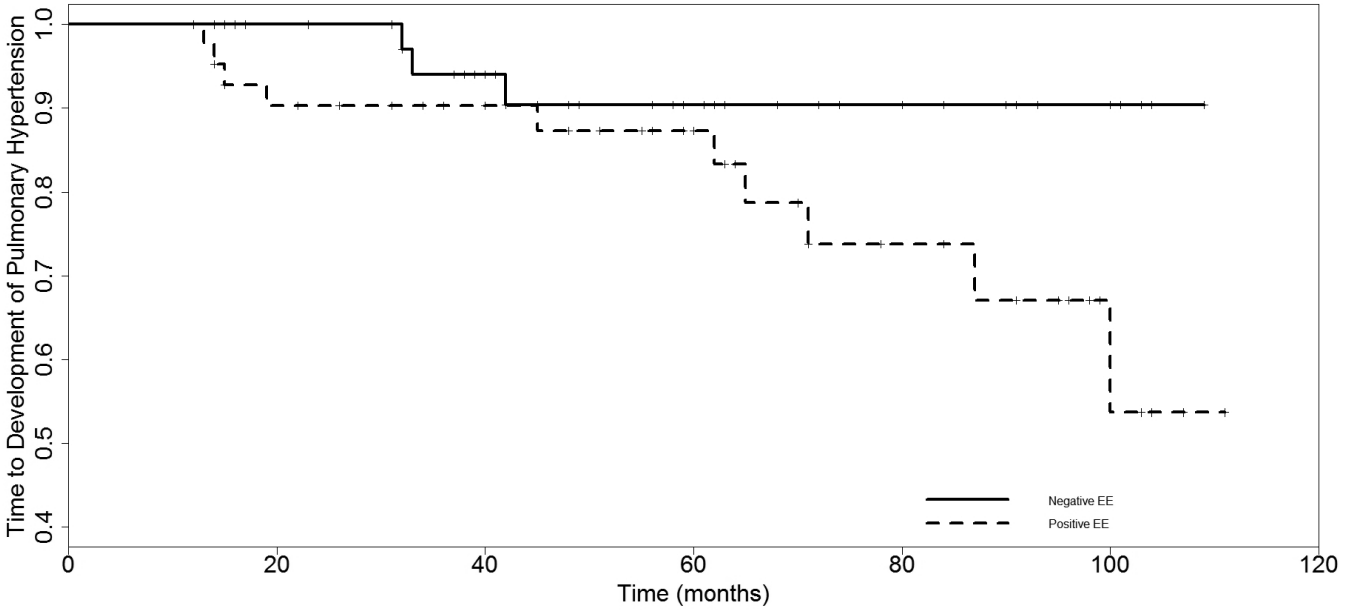

Figure 2. Time to development of pulmonary hypertension (PH) in patients grouped by exercise echocardiogram (EE) result. Patients were stratified based on EE result into the positive EE group (dashed line) and negative EE group (solid line). PH was defined by right heart catheterization > 25 mmHg. Patients in the positive EE group continued to develop PH over time. In the negative EE group, several patients developed PH early on, but this leveled off over time (p = 0.06).

Table 4. Outcome of 33 patients with positive exercise echocardiograms (EE) who did not develop resting pulmonary hypertension.

Positive EE Groups	n (%)
Persistently positive EE	22 (67)
Persistently+ EE and exercise PH on RHC	18 (55)
EE normalized	5 (15)
Echo remained normal (no repeat EE)	6 (18)

Echo: resting echocardiogram; PH: pulmonary hypertension; RHC: right heart catheterization.

This study included 85 patients with SSc who were at increased risk for PH, without a diagnosis of PH at time of entry. To our knowledge, this is the largest cohort of high-risk SSc patients with followup EE and clinical outcome data over an average duration of 5 years. Previous studies have shown an association between abnormal EE and detection of PH in SSc[7,14,18], and it has been recommended that EE be considered in patients with SSc[16,19]. However, there have been few studies that have followed SSc patients with abnormal EE over time to determine PH outcomes. Codullo, *et al*[20] found that a change in RVSP > 18 mmHg with exercise was significantly associated with the development of PH over 3.5 years of followup, with a sensitivity of 50% and specificity of 90%. They identified 6 patients out of 170 (3.5%) who developed incident resting PH (3 PAH, 2 PVH, 1 Group III PH) at followup. Our study results also showed that positive EE was associated with the development of PH, but not necessarily PAH. Voilliot, *et al*[21] followed 40 patients with SSc who had previously undergone EE. They found that 28% (11 patients) developed resting PH over a 2-year followup period, and all those patients had exercise-induced PH assessed by EE at index evaluation. They also noted that patients without an abnormal increase on EE were at very low risk for future PH. Our current study supports this finding that a persistently negative EE may identify patients at low risk for future PH.

There were no significant differences in antibody profiles among patients with a positive EE compared to patients with a negative EE, although a nucleolar antibody pattern and ACA are associated with an increased risk of PAH in SSc[22,23]. In our previous study, the amount of increase in RVSP during exercise was significantly greater in patients with ACA and antinucleolar antibodies compared to patients with an anti-Scl-70 antibody[14]. Although not statistically significant, there was a similar trend in this study toward more patients with positive EE being ACA- or antinucleolar antibody–positive, as compared to anti-Scl-70 antibody–positive. However, there were also no significant antibody differences between the patients who did and did not develop PH, or between patients who developed PAH compared to those who developed PVH. This may be attributable to the overall small sample size of patients who developed PH, but it is consistent with prior studies[20] that have not shown significant antibody differences between patients who did and did not develop PH.

Our study does have some important limitations. This was a single-center study, and reproducibility of these findings across other cohorts remains unknown. Patients were

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followed by standard of care rather than strict followup study protocol. Therefore, patients underwent RHC only if they had a positive EE or if PH was clinically suspected, so we did not have RHC data on every patient enrolled in the study. It should be noted that a positive EE in our study was defined as a post-exercise RVSP increase of at least 20 mmHg over the resting RVSP. This was the same standard used in the initial study[14], but there is no standardized consensus on accepted cutoff values, making comparisons among studies more difficult. As in the initial study, 20 mmHg was chosen as a more conservative cutoff value than prior studies, such as Grünig, *et al*, which used 15 mmHg[13]. Finally, our patients exercised with a Bruce protocol treadmill test, but a review of EE revealed significant variability in the exercise methods used in different studies[18]. While we recognize the world of exercise PH is rapidly changing and our initial protocol is clearly now not state of the art, it is still valuable to report our findings. Importantly, not all patients with positive EE develop PH, and many do not even have significant changes in their clinical status over many years of followup, despite having persistently abnormal exercise physiology. A more in-depth examination of different echocardiographic measures that may be associated with PH may be important to assess in future studies.

In this prospective cohort study of patients with SSc who are at high risk for PAH, we found that a positive EE is a useful tool to predict the future development of resting PH, but not specifically PAH, because a positive EE was also associated with PVH. In addition, patients often have a persistently positive EE for years without progression to resting PH. Finally, a persistently negative EE may identify patients at low risk for future PH.

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