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The Submaximal Heart and Pulmonary Evaluation: A Novel Noninvasive Test to Identify Pulmonary Hypertension in Patients with Systemic Sclerosis

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Abstract

Objective—Pulmonary hypertension (PH) is a leading cause of death in patients with systemic sclerosis (SSc). Although right heart catheterization is the gold standard for diagnosing PH, it is an invasive test with associated risks. The submaximal heart and pulmonary evaluation (step test) is a noninvasive, submaximal stress test that could be used to identify patients with PH. The purpose of this study is to assess the correlation between change in end tidal carbon dioxide (ΔP_{ETCO2}) from rest to end-exercise on the step test and mean pulmonary artery pressure (mPAP) on RHC in SSc patients.

Methods—This is a retrospective cohort study of patients with limited or diffuse cutaneous SSc who were evaluated in an academic cardiology practice between November 2007 and November 2011 and underwent a step test and RHC. Statistical analysis was performed using Spearman's correlation and multivariable linear regression.

Results—679 charts were reviewed. Nineteen SSc patients who underwent a step test and RHC were included. ΔP_{ETCO2} was negatively correlated with mPAP ($r = -0.82$, p-value < 0.0001). In a multivariable linear regression model evaluating the relationship between ΔP_{ETCO2} and mPAP, controlling for age, sex, time between and order of step test and RHC, ΔP_{ETCO2} remained the only variable statistically significantly associated with mPAP (p-value < 0.001). The step test had a sensitivity of 100%, specificity of 75%, PPV of 93.8%, and NPV of 100% for the diagnosis of PH.

Conclusions—ΔP_{ETCO2} on the step test has a strong, statistically significant negative correlation with mPAP on RHC.

Pulmonary hypertension (PH) has a prevalence of 8 to 12% in patients with systemic sclerosis (SSc) (1, 2) and is a leading cause of death in this population (3). Right heart catheterization (RHC) is the gold standard for diagnosing PH, defined as a mean pulmonary arterial pressure (mPAP) ≥25 mmHg (4). However, RHC is an expensive and invasive test with significant associated risks. Because of these risks, noninvasive methods of screening for PH are commonly used, such as serial pulmonary function testing (PFT) and

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transthoracic echocardiogram (TTE). Estimation of the pulmonary artery systolic pressure (PASP) on TTE requires the presence of a tricuspid regurgitant jet. However, there is no single accepted cutoff point for an abnormal PASP. In addition, there are many limitations of TTE in its estimation of pulmonary artery pressures. Tricuspid regurgitant jets are unanalyzable in as many as 41% of patients with SSc (5). There are variable correlations between PASP on TTE and pulmonary artery pressure measurements on RHC, with some correlations as poor as r = 0.31 (p-value = 0.13) (4). Studies that have examined the degree of difference between echocardiographic *estimates* of pulmonary artery pressure and RHC *measurements* of pulmonary artery pressure have found differences ranging from 3 to 38 mmHg (4, 6). Correlations are particularly poor for patients with pulmonary disease.

The submaximal heart and pulmonary evaluation (step test) is a noninvasive, submaximal stress test that can be used to identify patients with PH (7). It consists of a 5.5 inch high step that patients step up and down on for 3 minutes. During the test, heart rate, heart rhythm, breathing pattern, and gas exchange are monitored using a simplified gas exchange system (SHAPE Medical Systems, Inc, St. Paul, MN). This portable gas exchange system has been designed for submaximal exercise testing and contains built-in automated temperature, barometric pressure, and humidity corrections (8). The entire test lasts for 6 minutes: 2 minutes of baseline monitoring, 3 minutes of step exercise, and 1 minute of recovery. It is "submaximal" because subjects are not required to reach VO_2 max as they are in a full cardiopulmonary exercise test. This submaximal level of exercise is significantly easier for patients with cardiopulmonary or musculoskeletal disease to achieve.

The step test measures end tidal carbon dioxide (P_{ETCO2}), which is the partial pressure of CO_2 measured at end exhalation (9). P_{ETCO2} is positively correlated with cardiac output and pulmonary blood flow, and negatively correlated with pulmonary vascular resistance and the minute ventilation/CO_2 production (V_E/V_{CO2}) ratio (7, 10). Patients without PH can augment their cardiac output and pulmonary blood flow in response to exercise, leading to increased perfusion of alveoli, which in turn leads to an increase in P_{ETCO2} (7, 11). Patients with PH, on the other hand, are unable to increase their cardiac output or pulmonary blood flow in response to exercise, leading to ventilation/perfusion (V/Q) mismatch, which in turn leads to a decrease in P_{ETCO2} (7, 11).

In a previous study of 40 patients with PH and 25 healthy controls, the step test was able to distinguish PH patients from healthy controls (7). However, of the 40 patients with PH, only 8 were identified as having unspecified connective tissue disease. Since PH can behave differently in patients with different connective tissue diseases -- in SSc versus systemic lupus erythematosus, for example (12) -- it remains unknown how the step test might perform in patients with SSc. The aim of this study, therefore, was to assess the performance of the step test in a group of SSc patients by evaluating the strength of the correlation between change in end tidal carbon dioxide (ΔP_{ETCO2}) from rest to end-exercise on the step test, and mPAP as measured by RHC.

PATIENTS AND METHODS

This is a retrospective cohort study of patients with limited or diffuse cutaneous SSc who underwent a step test and RHC as part of clinical care or part of an observational study. Charts of patients who were evaluated by a PH specialist in an academic cardiology practice between November 2007 and November 2011 were reviewed. Patients were included in this study if they had received a diagnosis of limited or diffuse cutaneous SSc from a rheumatologist, and had undergone both a step test and RHC. Descriptive data were collected, as were data on medication use at the time of the step test and the time of RHC. This study was approved by the Institutional Review Boards at Hospital for Special Surgery and Weill Cornell Medical College.

We performed a Spearman's correlation between mPAP on RHC and ΔP_{ETCO2} from rest to end-exercise on the step test. In patients for whom TTE and PFT results were available, we also performed a Spearman's correlation between mPAP on RHC and PASP on TTE, as well as between mPAP on RHC and the forced vital capacity:diffusion capacity (FVC/DLCO) ratio on PFTs. We performed univariate analyses to evaluate the relationship between potentially important covariates and mPAP. We then performed a multivariable linear regression to evaluate the relationship between ΔP_{ETCO2} and mPAP, controlling for these potential confounding variables. All of the independent variables that attained a p-value < 0.2 in the univariate analyses were included in the final model, as were age and sex. In addition, we calculated the performance characteristics of the step test, TTE, and PFTs in this patient population, using RHC as the gold standard for PH diagnosis. Four millimeters of mercury was used as the cut-off point between normal and abnormal ΔP_{ETCO2}, as reported in the literature (13). All analyses were performed using STATA (version 12.1, College Station, Texas, USA).

RESULTS

Of the 679 charts reviewed, 71 patients had received a diagnosis of limited or diffuse cutaneous SSc from a rheumatologist. Thirty-four of these patients had undergone a RHC, and 19 of these patients had also undergone a step test and were therefore included in this study. The average age of patients was 61 years (SD 12.5). Eighty-four percent were female, 76% identified themselves as white, 84% had limited cutaneous SSc, and 79% had PH. Of the 15 patients who had PH, 73% had World Health Organization (WHO) Group 1 PH, or pulmonary arterial hypertension. Patients were screened for thromboembolic disease as clinically indicated; none had chronic thromboembolic PH. In patients for whom antibody results were available, 93% were ANA positive, 47% were anti-centromere positive, and 6% were anti-Scl-70 positive. One-hundred percent of patients had a history of Raynauds, 94% had sclerodactyly, and 37% had interstitial lung disease (ILD). Few patients were on immunomodulatory medications. However, considerable percentages were on medications for PH (Table 1).

ΔP_{ETCO2} on the step test was strongly negatively correlated with mPAP on RHC ($r = -0.82$, p-value < 0.0001). PASP on TTE was positively correlated with mPAP on RHC ($r = 0.74$, p-value = 0.0004). One patient with PH on RHC had an unanalyzable tricuspid regurgitant jet

on TTE and could not be included in this analysis. The FVC/DLCO ratio was positively correlated with mPAP on RHC (r = 0.53, p-value = 0.034), although the DLCO was not linearly correlated with mPAP on RHC (r = −0.33, p-value = 0.21). ΔP_{ETCO2} on the step test was strongly negatively correlated with pulmonary vascular resistance (PVR) on RHC (r = −0.82, p-value = 0.0002) (Table 2). When including only patients with PH (n = 15) in the analysis, ΔP_{ETCO2} on the step test remained strongly negatively correlated with mPAP on RHC (r = −0.72, p-value = 0.0026). PASP on TTE remained positively correlated with mPAP on RHC (r = 0.67, p-value = 0.0092). However, the one patient in this study who had an unanalyzable tricuspid regurgitant jet on TTE but did have PH on RHC could not be included in the analysis. The correlation between the FVC/DLCO ratio and mPAP on RHC was weak and not statistically significant (r = 0.16, p-value = 0.62). ΔP_{ETCO2} on the step test remained strongly negatively correlated with PVR on RHC (r = −0.77, p-value = 0.0012). When we performed a Spearman's correlation between ΔP_{ETCO2} on the step test and mPAP on RHC in only those patients who performed the step test in a non-experimental setting (n = 14), the correlation was still significant, although slightly weaker (r = −0.72, p-value=0.003).

The only variables that attained a p-value < 0.2 in the univariate analyses were ΔP_{ETCO2} and days between and order of the step test and RHC (Table 2). In the multivariable linear regression model evaluating the relationship between ΔP_{ETCO2} and mPAP, with mPAP as the dependent variable, and controlling for age, sex, and days between and order of the step test and RHC, ΔP_{ETCO2} remained the only variable statistically significantly associated with mPAP (β = −1.91, p-value = 0.001).

Using RHC as the gold standard for the diagnosis of PH, the step test had a sensitivity of 100%, specificity of 75%, positive predictive value (PPV) of 93.8%, and negative predictive value (NPV) of 100%. The step test performed better than both TTE and PFTs in this cohort of SSc patients with a high prevalence of PH (Table 3).

DISCUSSION

This is the first study to investigate the step test in a cohort of SSc patients. We found that ΔP_{ETCO2} on the step test has a very strong, statistically significant negative correlation with mPAP on RHC, and that ΔP_{ETCO2} on the step test is better correlated with mPAP on RHC than are PASP on TTE or FVC/DLCO on PFTs. We also found that the step test has excellent sensitivity, specificity, PPV, and NPV for the diagnosis of PH in this patient population with a high prevalence of PH.

There are several strengths of this study. First, it evaluated a novel technology that has the potential to fulfill an important unmet need as an accurate, noninvasive technique to screen for PH in many patients with SSc. TTEs are often inadequate screening tools for PH in the SSc population, as tricuspid regurgitant jets are frequently unanalyzable in these patients. Indeed, even in this relatively small study, one patient who had known PH on RHC had an unanalyzable tricuspid regurgitant jet on TTE -- and therefore a non-diagnostic TTE. This underscores the insufficiencies of TTE as a screening test for PH. Moreover, the step test performed well in the entire cohort of SSc patients as well as in the subgroup of SSc patients

with PH, unlike PFTs, which failed to correlate significantly with mPAP on RHC in the SSc patients with PH in this study. Further, the step test provides physiologic information on patients' breath-to-breath gas exchange, and these data are gathered at a submaximal exercise threshold. Therefore, achievement of VO_2 max is not required, and even SSc patients with poor cardiovascular fitness or musculoskeletal disease are likely able to perform the step test.

There are some limitations of this study. It was retrospective, with a relatively small sample size. Several patients in this study received their rheumatologic care at other institutions, and we therefore did not have access to their office charts for more detailed clinical information. For some patients in this study, a long time had elapsed between the step test and RHC, a period during which changes in management could have occurred, thereby affecting results on the subsequent test. However, we accounted for time between the step test and RHC in our multivariable linear regression model, which did not affect the strength of the association between ΔP_{ETCO2} and mPAP. Of the 7 patients with ILD, only 1 had interval progression between the step test and RHC; 5 had no interval progression (1 was unknown). In addition, discordance in medication use between the step test and RHC was not statistically significant in univariate analyses, and therefore was not included in the multivariable model. Patients were identified from an academic cardiology practice with a high prevalence of PH. However, this is an SSc population in which the step test could be particularly useful. Most of the patients in this study received the step test as part of their routine clinical care, as it is a test which is used in clinical practice by some PH specialists. Therefore, there was possible confounding by indication in patients who underwent the step test, as perhaps only those with the worst PH were offered the test. However, when we performed correlations limited only to those with PH, or to those patients receiving the step test as part of clinical care, the correlations were weaker, but remained statistically significant. This suggests that the diagnostic utility of the step test is not limited to those with the most severe PH, and that these findings are not the result of a biased clinical sample.

CONCLUSION

This study shows that the step test, a noninvasive, submaximal stress test, has excellent correlation with RHC measurement of PH in patients with SSc. Larger prospective studies investigating the ability of the step test to identify SSc patients with and without PH are needed. In addition, the utility of the step test as a screening test for PH in a cohort of SSc patients not enriched for PH should be established. The step test has significant clinical potential as a tool for evaluation of PH in the SSc population.

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Significance and Innovation

- This was the first study to investigate the ability of this step test to identify pulmonary hypertension in a cohort of systemic sclerosis patients.
- We found that change in end tidal carbon dioxide (ΔP_{ETCO2}) as measured by the step test has a very strong, statistically significant negative correlation with mean pulmonary artery pressure (mPAP) on right heart catheterization (RHC), and that ΔP_{ETCO2} on the step test is better correlated with mPAP on RHC than are pulmonary artery systolic pressure on transthoracic echocardiogram (TTE) or the forced vital capacity:diffusion capacity (FVC/DLCO) ratio on pulmonary function testing (PFTs).
- We found that the step test has excellent sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of pulmonary hypertension in this cohort of systemic sclerosis patients, and that the step test performed better than both TTE and PFTs in this systemic sclerosis cohort with a high prevalence of pulmonary hypertension.

Table 1

Patient Characteristics, Test Results, and Medications

Age – yr, mean ± SD	61 ± 12.5
Female sex – no. (%)	16/19 (84)
White race – no. (%)	13/17 (76)
Limited cutaneous SSc – no. (%)	16/19 (84)
Disease duration – yr, mean ± SD	15 ± 11.9
Pulmonary hypertension – no. (%)	15/19 (79)
WHO group 1 (pulmonary arterial hypertension)	11/15 (73)
WHO group 2 (pulmonary venous hypertension)	0 (0)
WHO group 3 (PH due to lung disease)	1/15 (7)
Mixed	3/15 (20)
Functional class – no. (%)	
I	3/19 (16)
II	3/19 (16)
III	13/19 (68)
ANA positive – no. (%)	14/15 (93)
Anti-centromere antibody positive – no. (%)	7/15 (47)
Anti-topoisomerase I (Scl-70) antibody positive – no. (%)	1/16 (6)
Raynaud's	19/19 (100)
Digital ulcerations	9/18 (50)
Renal crisis	1/16 (6)
Sclerodactyly	17/18 (94)
Interstitial lung disease	7/19 (37)
Gastroesophageal reflux disease	16/18 (89)
Esophageal dysmotility	9/16 (56)
Calcinosis	6/12 (50)
Telangiectasias	16/16 (100)
Myositis	1/17 (6)
Arthritis	8/19 (42)
Lower extremity joint contractures	2/17 (12)
Tobacco use	
Never	11/19 (58)
Former	8/19 (42)
Obstructive sleep apnea	2/19 (11)
Time between step test & RHC – days, median (min, max) (n = 7)	141 (29, 291)
Time between RHC & step test – days, median (min, max) (n = 12)	368 (33, 777)
RHC mPAP – mmHg, median (min, max)	39 (10, 58)
RHC mean right atrial pressure – mmHg, median (min, max)	8 (0, 20)
RHC pulmonary capillary wedge pressure – mmHg, median (min, max)	8.5 (2, 15)
RHC cardiac output – L/min, median (min, max)	3.85 (1.97, 8.29)
RHC pulmonary vascular resistance – Wood units, median (min, max)	8.91 (2.58, 21.61)

Step test ΔP_{ETCO2} – mmHg, median (min, max)	−3.6 (−9.6, 11.7)
TTE PASP – mmHg, median (min, max)	57.6 (25.1, 97)
PFT DLCO – %predicted, median (min, max)	38.5 (26, 70)
PFT FVC/DLCO – median (min, max) (n = 16)	2.11 (1.24, 3.72)

Medication	**Use at Step Test (N = 19)**	**Use at RHC (N = 17)***
Corticosteroids – no. (%)	3 (16)	3 (18)
Cyclophosphamide – no. (%)	0 (0)	0 (0)
Methotrexate – no. (%)	0 (0)	0 (0)
Mycophenolate mofetil – no. (%)	2 (11)	1 (6)
Azathioprine – no. (%)	1 (5)	1 (6)
Hydroxychloroquine – no. (%)	3 (16)	2 (12)
Calcium channel blocker – no. (%)	7 (37)	5 (29)
Endothelin receptor antagonist – no. (%)	7 (37)	7 (41)
Phosphodiesterase 5 inhibitor – no. (%)	12 (63)	13 (76)
Prostacyclin analogue – no. (%)	3 (16)	2 (12)
Supplemental oxygen – no. (%)	8 (42)	8 (47)
Aspirin – no. (%)	8 (42)	6 (35)
Warfarin – no. (%)	8 (42)	6 (35)
Enoxaparin – no. (%)	1 (5)	1 (6)

* Medication lists at the time of RHC were unavailable for 2 patients

Table 2

Spearman's Correlations and Univariate Associations with mPAP

Test	Spearman's Correlation with mPAP on RHC	p-value
Step test: ΔP_{ETCO2}	−0.82	0.0001
TTE: PASP	0.74*	0.0004
PFT: FVC/DLCO	0.53	0.034
PFT: DLCO	−0.33	0.21

Test	Spearman's Correlation with ΔP_{ETCO2} on Step Test	p-value
RHC mean right atrial pressure	−0.39	0.10
RHC cardiac output	0.39	0.11
RHC pulmonary vascular resistance	−0.82	0.0002

Independent Variable	p-value
ΔP_{ETCO2}	0.001
Age	0.43
Sex	0.57
Days between and order of step test & RHC	0.08
Discordance in calcium channel blocker use b/w step test & RHC	0.22
Discordance in endothelin receptor antagonist use b/w step test & RHC	0.42
Discordance in phosphodiesterase 5 inhibitor use b/w step test & RHC	0.22
Discordance in prostacyclin analogue use b/w step test & RHC	0.94
Discordance in aspirin use b/w step test & RHC	N/A**
Discordance in warfarin use b/w step test & RHC	0.50
Discordance in enoxaparin use b/w step test & RHC	N/A**
Discordance in supplemental oxygen use b/w step test & RHC	0.92

* Does not include one patient in this study who had an unanalyzable tricuspid regurgitant jet on TTE but did have PH on RHC

** None of the patients experienced discordance in aspirin or enoxaparin use between step test and RHC

Table 3

Performance Characteristics of Tests to Identify PH

Test	Sensitivity*	Specificity*	PPV*	NPV*
Step test	100%	75%	93.8%	100%
ΔP_{ETCO2} < 4 mmHg				
TTE	80%	25%	80%	25%
PASP > 35 mmHg				
PFTs	91.7%	75%	91.7%	75%
FVC/DLCO > 1.6				

*Using RHC as the gold standard for diagnosis of PH (mPAP ≥ 25 mmHg)