

Cardiopulmonary Exercise Testing with Right-heart Catheterization in Patients with Systemic Sclerosis

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ABSTRACT. Objective. To examine the role of cardiopulmonary exercise testing with right-heart catheterization (CPET/RHC) in patients with systemic sclerosis (SSc) with potentially multifactorial exertional limitation.

Methods. This was a single-center retrospective cohort study of patients with SSc referred for CPET/RHC.

Results. A total of 19 patients with SSc [subtypes: 10 limited, 5 diffuse, 1 systemic lupus erythematosus (SLE)/SSc overlap, and 3 with no subtype specified in the medical record] underwent CPET/RHC testing from February 2003 to February 2008. Of these patients, the primary limitations to exercise were found to be ventilatory (n = 6), deconditioning/cardiovascular (n = 6), pulmonary vascular (PVL; n = 3), and exercise-induced left ventricular diastolic dysfunction (exercise-LVDD; n = 4). No prior physical examination, pulmonary function test, imaging, or echocardiographic data reliably predicted the etiology of exercise limitation determined by CPET/RHC. Vital capacity and ventilatory equivalent for CO₂ did not differ during CPET testing between PVL and exercise-LVDD, limiting the utility of CPET alone for discriminating these etiologies of dyspnea. Exercise alveolar-arterial oxygen gradient was elevated in subjects shown to have PVL [median 48 mm Hg (interquartile range 45.3, 62.0)] compared to those with exercise-LVDD [26.0 (IQR 10.6, 36.0)] and deconditioning [13.9 (IQR 4.0, 16.4); p = 0.02]. Major therapeutic changes occurred in 11/19 (58%) subjects after CPET/RHC testing.

Conclusion. CPET/RHC testing in subjects with SSc and potentially multifactorial dyspnea adds potentially useful diagnostic information unavailable from noninvasive testing. (First Release June 15 2010; J Rheumatol 2010;37:1871–7; doi:10.3899/jrheum.091424)

Key Indexing Terms:

SYSTEMIC SCLERODERMA

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Cardiopulmonary disease is the leading cause of death among individuals with systemic sclerosis (SSc)^{1,2,3}. Therefore, dyspnea and exercise intolerance are concerning symptoms in any patient with SSc. Determining the etiology of exercise limitation in patients with SSc is complicated by multiorgan involvement of the disease, with SSc potentially causing interstitial lung disease, pulmonary arterial hypertension (PAH), left ventricular dysfunction, and/or peripheral myositis⁴. Due to the poor prognosis associated with cardiopulmonary involvement of SSc and the availability of therapies for these manifestations^{5,6,7}, differentiation of the cause of dyspnea in SSc is increasingly important.

Cardiopulmonary exercise testing (CPET) is a useful modality in cases of unexplained dyspnea^{8,9,10}, particularly in patients with multiple comorbidities involving different organ systems. CPET can be helpful in differentiating

between cardiovascular, ventilatory or pulmonary vascular exertional limitation. The addition of a right-heart catheter (RHC) significantly increases the ability to discriminate PAH from left ventricular diastolic dysfunction (exercise-LVDD)^{11,12}, manifestations recognized as increasingly common in SSc^{13,14}.

We evaluated the role of CPET combined with right-heart catheterization (CPET/RHC) in SSc patients with potentially multifactorial exercise limitation and dyspnea. We hypothesized that without functional metabolic and hemodynamic assessments, initial noninvasive testing would not reliably discern the etiology of exertional dyspnea in these SSc patients with multiple organ involvement. In addition, we attempted to define whether measures derived from preliminary testing and CPET without RHC might reliably discriminate a pulmonary vascular limitation from pulmonary venous hypertension due to exercise-LVDD. Last, we determined the clinical influence of CPET/RHC in altering the treatment plan of SSc patients undergoing such testing.

MATERIALS AND METHODS

Patients. A retrospective chart review of test results for all SSc patients who underwent CPET/RHC evaluation at our institution over the 5-year period February 2003 to February 2008 is the basis for this report. The

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Institutional Review Board approved all data collection procedures for this study and waived informed consent for this retrospective review.

Patients with SSc were referred to the Boston Medical Center Pulmonary Hypertension Center for evaluation of unexplained dyspnea on exertion. Subjects were subsequently scheduled for CPET/RHC testing based on preliminary evaluation that failed to define a most probable explanation for their symptoms, and raised the possibility of pulmonary vascular disease (Table 1). The majority of patients underwent chest radiography, high resolution chest tomography, echocardiogram, and pulmonary function testing prior to CPET/RHC testing. The diagnosis of SSc per American College of Rheumatology criteria was confirmed by clinical evaluation of a board-certified rheumatologist. Documentation of serologic testing was available for 8/19 subjects and therefore was not included in this analysis.

CPET protocol. Study personnel for CPET/RHC included a pulmonary Attending and Fellow, a registered nurse, and a registered respiratory therapist. All patients provided informed consent for the CPET/RHC procedure. Patients were escorted to the pulmonary function test laboratory where a radial arterial blood gas was drawn. Patients underwent pulmonary function testing (Viasys Encore; Cardinal Health, Dublin, OH, USA) including spirometry, maximal voluntary ventilation, and DLCO testing. Patients were then escorted to a designated catheterization suite, where a RHC was placed through an 8.5 French jugular venous introducer under sterile conditions; RHC placement was confirmed by chest radiograph prior

to CPET. Baseline supine RHC hemodynamic values were obtained [central venous pressure (CVP), right ventricular pressure (RVP), pulmonary arterial pressure (PA_{mean}), pulmonary capillary wedge pressure (PCWP), cardiac output and cardiac index via thermodilution (CO and CI), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR)]. Patients returned to the pulmonary function laboratory, where baseline blood pressure, heart rate, oxygen saturation, EKG, and identical right-heart catheter hemodynamic values were repeated after the patient had been properly positioned on an upright bicycle ergometer. All measurements were obtained using the Viasys Encore system with integrated continuous EKG monitoring (Max-1 EKG; Marquette Medical, Milwaukee, WI, USA). Patients were fitted with headgear to support a flow sensor and an oximeter to measure continuous oxygen saturation. After a 1-min warm-up phase at 60 rpm and no resistance, the subject began a graded exercise program with a work increase of 5–10 w/min, depending on baseline conditioning status, with a goal rate of 60 rpm. Manual blood pressure measurements and RHC hemodynamic values were obtained every 2 min during exercise, with PCWP measured at end exhalation via analysis of the RHC pressure tracings. 12-lead EKG monitoring was continuous. Patients exercised until they were unable to maintain 60 rpm or until experiencing symptoms and/or abnormal vital signs that necessitated discontinuation of the procedure. Criteria for terminating CPET prior to patient request were based on institutional policy and included ischemic chest pain or EKG changes, complex ectopy, second or third degree heart block, fall in systolic blood pressure (SBP) > 20 mm Hg, systolic blood pressure \geq 250, diastolic blood pressure \geq 120 mm Hg, oxygen saturation < 85%, sudden pallor, loss of coordination, mental status changes, presyncope, or signs of respiratory failure. Patients whose studies were not terminated for any of these complications continued into recovery mode, cycling at no resistance for 2 min. At this time, a second radial arterial blood gas sample was obtained. Anaerobic threshold was determined by the V-slope method¹⁵. If no clear change in slope was seen, the R value or ventilatory equivalent methods were utilized.

Diagnostic classifications and definitions. Diagnostic classifications derived from the CPET/RHC analysis by the attending pulmonary physician of record at the time of testing were utilized as the primary outcome for this study. The original CPET/RHC-diagnosed etiologies for exercise limitation were classified for study purposes as “pulmonary vascular limitation” (PVL), “left ventricular diastolic dysfunction” (LVDD), “ventilatory limitation” (restrictive lung disease), or “deconditioning/cardiovascular limitation.” CPET/RHC diagnoses at our institution were determined by combining guidance from algorithms proposed by Wasserman, *et al*¹⁵ with the hemodynamic results from the RHC. For example, these algorithms suggest a diagnosis of PVL in subjects with decreased maximal VO_2 and anaerobic threshold with elevated ventilatory equivalent for CO_2 (VE/VCO_2); additionally, these subjects should have no evidence of pulmonary venous hypertension (PCWP < 18) on RHC. LVDD was considered for similar CPET findings, except with echocardiographic evidence of normal ejection fraction (\geq 50%) and RHC showing peak exercise-PCWP \geq 18 mm Hg and a pulmonary artery-diastolic pressure to-PCWP gradient \leq 5 mm Hg. Ventilatory limitations were considered for patients with low VO_2 and a low breathing reserve. Deconditioning was defined as a low maximum VO_2 without evidence for ventilatory, pulmonary vascular, or left ventricular abnormalities seen with CPET or RHC. A cardiovascular limitation was diagnosed for subjects with a low maximum VO_2 without evidence for ventilatory, pulmonary vascular, or hemodynamic abnormalities seen with CPET or RHC, but with an abnormal resting echocardiogram. Given similar CPET and RHC findings, subjects with deconditioning and cardiovascular limitation diagnoses were combined for purposes of analysis. Three attending physicians trained in pulmonary and critical care medicine were responsible for CPET readings during the study. For the purposes of the study, these CPET were then reread by an independent reviewer (MI) blinded to the initial readings — these readings agreed with the initial diagnostic assessment with a kappa statistic of 0.93 (95% CI 0.79–1.0).

SSc was subclassified into limited, diffuse, and scleroderma overlap

Table 1. Baseline characteristics of study subjects (n = 19).

Variable	N
Age, mean \pm SD, yrs	51.3 \pm 13.5
Male	5
Female	14
BMI, mean \pm SD, kg/m ²	25.1 \pm 3.6
Reasons for CPET/RHC referral (some subjects had > 1 reason for referral)	
Dyspnea on exertion	19
Exertional oxygen desaturation	10
Abnormal P2 heart sound	7
Abnormal echocardiography: estimated PASP \geq 40mm Hg	6
DLCO deemed out of proportion to ILD	6
New York Heart Association class	
II	13
III	6
Other medical history	
Asthma	4
Myositis	3
Cardiomyopathy	1
Coronary artery disease	1
Chest radiograph	
Normal	14
Abnormal parenchyma	3
Abnormal cardiac silhouette	2
Computed tomography scan thorax	
Normal	1
Interstitial abnormalities	15
Left ventricular ejection fraction	
Normal (\geq 50%)	16
Abnormal (< 50%)	1
Echocardiogram estimated pulmonary artery systolic pressure	
Normal (< 40 mm Hg)	10
Abnormal (\geq 40 mm Hg)	6

* Some subjects had > 1 reason for referral. BMI: body mass index; CPET/RHC: cardiopulmonary exercise testing with right-heart catheterization; ILD: interstitial lung disease.

syndromes. EKG was defined as normal or abnormal (any abnormality with the exception of nonspecific T wave changes). Chest radiographs were classified as normal, abnormal lung parenchyma, or abnormal cardiac silhouette. Chest computed tomography (CT) scans were classified as normal or parenchymal abnormalities (a radiologist report of fibrosis, ground glass, pneumonitis, reticulo-nodular). Echocardiography results were classified from the cardiologist's final echocardiogram report as normal ($\geq 50\%$) or abnormal ($< 50\%$) left ventricular ejection fraction (EF), normal or abnormal diastolic function based on Doppler interrogation of the mitral inflow pattern (E/A ratio), and normal [estimated pulmonary artery systolic pressure (PASP) < 40 mm Hg] or abnormal (PASP ≥ 40 mm Hg) PASP calculated from the tricuspid regurgitant jet.

Statistics. SAS v 9.1 (SAS Inc., Cary, NC, USA) was utilized for all data analysis. Continuous variables were expressed as mean \pm standard deviations for normally distributed variables and median (interquartile range, IQR) for nonparametric variables. Due to the limited sample size and multiple nonparametric variables, Wilcoxon rank sum and Kruskal-Wallis testing were used for comparisons of continuous variables. Categorical variables were analyzed with chi-square or Fisher's exact testing, where appropriate. An alpha level less than 0.05 indicated statistical significance.

RESULTS

Baseline data. Twenty patients with SSc underwent CPET/RHC testing during the study timeframe. One patient was excluded from analysis due to unreliable CPET data resulting from secretions occluding the mouthpiece. Thus, 19 SSc patients were included in this analysis, including 10 patients with limited SSc, 5 with diffuse SSc, one with lupus/SSc overlap syndrome, and 2 without SSc subtype specified in the medical record. All subjects were referred for CPET/RHC for unexplained dyspnea on exertion and suspicion of PVL to exertion. Additional reasons for CPET/RHC referral and baseline subject data are listed in Table 1. Subjects with limited SSc were on average older than subjects with diffuse SSc (58.7 ± 14 vs 38.6 ± 4.7 yrs, respectively; $p = 0.04$). Otherwise, no baseline differences were observed between SSc subtypes. No complications occurred during CPET/RHC.

CPET test data. Subjects with limited SSc had a higher pre-

dicted FVC ($82.4 \pm 16\%$ vs $52 \pm 13\%$), higher predicted FEV1 ($85 \pm 15\%$ vs $57 \pm 15.7\%$) and lower FEV1/FVC ratio (0.76 ± 0.05 vs 0.85 ± 0.05) than subjects with diffuse SSc. No differences in diffusion capacity were observed between SSc subgroups. Supplementary Appendix Table 1 gives baseline pulmonary function test (PFT) data for all subjects.

Complete CPET and arterial blood gas measurements for all SSc subjects are listed in Supplementary Appendix Table 2. No significant differences were observed between limited and diffuse SSc subtypes for these tests. RHC data resting supine, resting upright, and while upright during peak exercise are shown in Table 2. No differences in cardiopulmonary hemodynamics were found between SSc subtypes.

Etiology of exercise limitation. The distributions of etiologies for exercise intolerance as determined by CPET/RHC testing were ventilatory limitation ($n = 6$), deconditioning/cardiovascular limitation ($n = 6$), LVDD ($n = 4$), and PVL ($n = 3$). All subjects with PVL to exercise were of the limited SSc subtype. Eight subjects (42%) had results showing additional, significant pathology on either CPET or RHC analysis that was not felt to be exercise-limiting, including severe ventilatory abnormalities in 6 subjects, elevated PCWP in 2 subjects, and elevated PA_{mean} in 2 subjects. Thus, 4 subjects had exercise-induced elevations in PA pressures that were not felt to be the primary etiology of exercise limitation as determined by combined analysis of CPET and RHC testing.

At baseline, no clinical information acquired prior to CPET/RHC was predictive of the CPET/RHC-derived etiology of exercise intolerance or dyspnea (Table 3 shows data for individual subjects, Table 4 shows data for the study population). This included the indication for CPET/RHC referral, New York Heart Association (NYHA) class, resting echocardiographic values (PASP, diastolic function, left ventricular ejection fraction), pulmonary function test results, and imaging data (chest radiograph, CT).

Table 2. Summary right-heart catheter hemodynamic data recorded at rest and during peak exercise.

Measurement	Resting Supine, N	Resting Upright, N	Peak Exercise Upright, N
CVP, mm Hg	5.9 ± 2.5 , 16	1.6 ± 4.4 , 14	4.4 ± 5.7 , 16
PA_{mean} , mm Hg	20.6 ± 5.5 , 18	16.9 ± 4.2 , 14	30.1 ± 8.0 , 18
PCWP, mm Hg	9.6 ± 4.1 , 16	5.5 ± 4.2 , 14	12.6 ± 7.0 , 16
Cardiac output, l/min	5.7 ± 1.1 , 18	4.9 ± 1.2 , 14	12.0 ± 3.2 , 18
PVR, dyn-s/cm ⁵	166 ± 59 , 18	189 ± 69 , 14	133 ± 50 , 17
SVR, dyn-s/cm ⁵	1302 ± 347 , 18	1507 ± 336 , 14	761 ± 185 , 17

CVP: central venous pressure; PA_{mean} : mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance.

Table 3. Comparison of the clinical abnormalities apparent prior to cardiopulmonary exercise testing/right-heart catheterization (CPET/RHC) with data obtained from CPET/RHC and etiology of exercise limitation as determined by combined CPET/RHC analysis.

Patient	Indication for CPET/RHC	DLCO, %	HRR, bpm	VO ₂ max, %	AT, %	VE/VCO ₂ at AT	SpO ₂ , %	Value at Peak Exercise			PA _m /PCWP, mm Hg	Exercise Limitation: CPET/RHC
								O ₂ Pulse, %	BR, %	P(A-a)O ₂ , mm Hg		
1	O ₂ desaturation	46	-9	68	56	32.5	90	62	27	11.9	Normal	Deconditioning
2	O ₂ desaturation	63	-3	73	52	38.0	96	low	10	10.6	45/25	LV dysfunction
3	O ₂ desaturation P2	54	-12	53	39	42.0	93	55	21	45.3	29/1	Pulmonary vascular
4	Abnormal echo P2	34	20	18	11	62.0	96	18	22	1.0	22/9	Cardiovascular
5	Abnormal echo P2	40	18	47	36	31.0	94	66	2	36.0	38/19	Ventilatory
6	Abnormal echo P2	46	12	54	34	40.0	93	60	31	8.0	35/15	Pulmonary vascular
7	O ₂ desaturation Abnormal echo	59	-6	52	28	47.0	98	72	25	15.8	21/7	Deconditioning
8	O ₂ desaturation	59	6	61	42	34.0	97	71	28	29.8	35/18	LV dysfunction
9	O ₂ desaturation	18	31	32	19	49.0	89	50	33	62.0	34/10	Pulmonary vascular
10	O ₂ desaturation	56	4	43	44	37.0	98	55	28	4.0	18/4	Deconditioning
11	O ₂ desaturation, presyncope	52	-14	49	28	49.0	98	66	5	3.5	25/NA	Ventilatory
12	P2, abnormal echo	55	24	33	23	38.0	94	45	42	NA	28/12	Deconditioning
13	Progressive DOE	91	1	75	57	26.0	98	84	32	16.4	20/8	Deconditioning
14	Progressive DOE, abnormal echo	76	0	44	33	42.0	97	low	0	23.0	33/12	Ventilatory
15	Progressive DOE, O ₂ desaturation, P2	37	32	54	25	56.0	96	73	7	48.0	29/6	Ventilatory
16	Progressive DOE	55	-26	91	58	39.0	96	82	5	35.1	40/11	Ventilatory
17	Progressive DOE, O ₂ desaturation	54	-11	81	60	31.0	96	78	19	36.0	39/22	LV dysfunction
18	Progressive DOE	69	-7	56	36	37.0	98	56	67	26.0	34/22	LV dysfunction
19	Progressive DOE, P2	69	18	45	32	41.0	98	67	15	0.0	22/NA	Ventilatory

O₂ desaturation: exercise pulse oximetry decrease > 4 %; DOE: dyspnea on exertion; DLCO: diffusion capacity of lung for carbon monoxide; P2: abnormal 2nd heart sound on examination; abnormal echo: echocardiogram pulmonary pressure > 40 mm Hg; VO₂max%: % maximum predicted oxygen consumption; AT%: % anaerobic threshold; SpO₂: oxygen saturation at peak exercise during CPET; BR: breathing reserve; P(A-a)O₂: alveolar-arterial oxygen gradient at peak exercise; VE/VCO₂: ventilatory equivalent for CO₂ at anaerobic threshold; PA_m/PCWP: mean pulmonary arterial pressure and pulmonary capillary wedge pressure at peak exercise; exercise limitation: final assessment of findings from combined CPET/RHC; NA: value not available; if value is unavailable, available interpretation of data may be included in place of value.

Specifically, exertional hypoxemia detected by outpatient transcutaneous oximetry prior to CPET testing was not an accurate predictor of exercise-induced hypoxemia. The correlation between pulse oximetry in clinic and during the CPET was poor (Pearson $r = 0.28$, $p = 0.28$), with only 5/10 instances of abnormal desaturation seen with clinic oximetry associated with an abnormal A-a gradient during exercise. Resting echocardiography results also did not coincide with CPET/RHC data: 4/6 (66%) subjects with a ventilatory limit to exertion were found to have a resting echocardiogram demonstrating elevated PA pressures, although only one of these patients was found to have elevated PA_{mean} during CPET/RHC. In contrast, only 50% of patients meeting the study criteria for a pulmonary vascular limitation showed elevated PASP on resting echocardiography. Also, despite 5 subjects with elevated PCWP during CPET/RHC, no subject was found to have abnormal diastolic function by resting echocardiography. Imaging and pulmonary function testing were similarly unrevealing: all but one subject had

evidence of interstitial lung disease on CT scan and there were no significant differences in baseline PFT measurements — including DLCO — according to final diagnosis of exertional limitation by CPET/RHC.

Table 4 demonstrates that significant differences between CPET/RHC diagnostic categories were seen for breathing reserve [median breathing reserve for deconditioning/cardiovascular limit: 28 (IQR 25, 32) vs pulmonary vascular: 31 (IQR 21, 33) vs exercise-LVDD: 24 (IQR 15, 48) vs ventilatory limitation: 5 (IQR 2, 7); $p = 0.01$] and P(A-a)O₂ at peak exercise [in mm Hg: deconditioning/cardiovascular limit: 12 (IQR 4, 16) vs ventilatory limit: 29.1 (IQR 3.5, 36.0) vs pulmonary vascular limit: 48.0 (IQR 45, 62) vs exercise-LVDD: 26.0 (IQR 10.6, 36.0); $p = 0.04$].

Major treatment changes occurred in 11/19 (58%) patients after CPET/RHC, including 5 who started or changed dosing of immunosuppressive therapy for interstitial lung disease, 2 who started pulmonary vasodilator therapy, 2 who started treatment for left ventricular dysfunction,

Table 4. Comparison of median values for selected pulmonary function test, echocardiogram, and cardiopulmonary exercise test measurements based on cardiopulmonary exercise test and pulmonary arterial catheter-derived diagnosis. All values represent median (interquartile range).

Measure	Deconditioning/ Cardiovascular Limitation, n = 6	Ventilatory Limitation, n = 6	Pulmonary Vascular Limitation, n = 3	Exercise LVDD, n = 4	p
Clinic exertional O ₂ sat, %	96 (94, 97)	92 (83, 97)	88 (87, 92)	91 (90, 93)	0.14
Echo PASP, mm Hg	28 (25, 39)	42 (32, 45)	28 (20, 36)	28 (20, 35)	0.50
VO ₂ maximum, % predicted	47 (33, 68)	48 (45, 54)	53 (32, 54)	67 (59, 77)	0.20
AT % VO ₂ , maximum predicted	36 (23, 56)	32 (28, 36)	34 (19, 39)	47 (39, 56)	0.35
Predicted FVC, %	61 (47, 79)	73 (58, 90)	74 (52, 101)	92 (74, 99)	0.21
Predicted FEV1, %	66 (47, 79)	76 (63, 95)	78 (53, 98)	93 (77, 102)	0.23
Predicted FEV1/FVC, %	83 (80, 86)	79 (72, 86)	76 (73, 79)	76 (72, 81)	0.22
O ₂ saturation, % peak	97 (94, 98)	97 (96, 98)	93 (89, 93)	97 (96, 98)	0.09
Predicted DLCO	56 (46, 59)	54 (40, 69)	46 (18, 54)	61 (57, 66)	0.28
% FVC/% DLCO	1.15 (0.87, 1.23)	1.35 (1.13, 1.64)	1.87 (1.13, 4.1)	1.43 (1.23, 1.56)	0.18
HRR, bpm	2.5 (-6, 20)	9 (-14, 18)	12 (-12, 31)	-5 (-9, -1.5)	0.77
Predicted O ₂ pulse	59 (45, 72)	67 (66, 73)	55 (50, 60)	71 (56, 78)	0.19
BR, %	28 (25, 32)	5 (2, 7)	31 (21, 33)	24 (15, 48)	0.01
RR, bpm	47 (32, 44)	52 (45, 62)	42 (39, 59)	49 (42, 55)	0.16
TV, l	1.61 (1.17, 1.69)	1.08 (0.93, 1.42)	0.98 (0.98, 1.56)	1.29 (1.1, 1.4)	0.40
V _d /V _t , rest	0.47 (0.34, 0.54)	0.45 (0.28, 0.48)	0.38 (0.37, 0.42)	0.29 (0.26, 0.29)	0.14
V _d /V _t , exercise	0.23 (0.18, 0.32)	0.26 (0.20, 0.31)	0.28 (0.20, 0.30)	0.19 (0.18, 0.20)	0.24
P(A-a)O ₂ , rest mm Hg	2.3 (0, 7)	13.1 (5.0, 21.3)	19.9 (15.3, 38.0)	11.7 (11.5, 29.0)	0.02
P(A-a)O ₂ , exercise	12 (4.0, 16)	29.1 (3.5, 36.0)	48.0 (45.3, 62.0)	26.0 (10.6, 36.0)	0.04
VE/VCO ₂	38 (33, 47)	42 (39, 49)	42 (40, 49)	37 (31, 38)	0.19
etCO ₂ at AT, mm Hg	36 (36, 41)	35.7 (30.5, 41.3)	32.8 (31.8, 36.6)	35.0 (32.6, 38.7)	0.70
etCO ₂ /VEVCO ₂	1.07 (0.88, 1.10)	0.82 (0.73, 0.98)	0.76 (0.67, 0.92)	0.95 (0.86, 1.25)	0.22

P value for between-groups Kruskal-Wallis testing. LVDD: left ventricular diastolic dysfunction; VO₂ max: maximum oxygen uptake; AT: anaerobic threshold; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; ratio: FVC/FEV1; O₂ saturation %, peak: oxygen saturation at peak exercise; DLCO: diffusion capacity of lung for carbon monoxide; HRR: heart rate reserve; BR: breathing reserve; RR: respiratory rate; TV: tidal volume; V_d/V_t: physiological dead space/total tidal volume ratio; P(A-a)O₂: alveolar-arterial oxygen gradient; VE/VCO₂: ventilatory equivalent for CO₂; etCO₂: end tidal CO₂; Echo PAP: pulmonary arterial pressure estimated by tricuspid regurgitant jet velocity on echocardiogram.

and 2 subjects with deconditioning who were prescribed a conditioning regimen.

DISCUSSION

This study evaluates the results of cardiopulmonary exercise testing utilizing invasive hemodynamic monitoring (CPET/RHC) in SSc patients with potentially multifactorial exercise limitation. We hypothesized that in select SSc patients with suspected pulmonary vascular disease, CPET/RHC would provide valuable data unavailable with a conventional evaluation, which would enable differentiation of multiple potential etiologies for exercise limitation⁴. Importantly, CPET/RHC was able to differentiate between exercise-induced left ventricular dysfunction, pulmonary vascular disease, and interstitial lung disease as the etiology of exercise intolerance in these subjects. These diagnoses were not accurately obtained with other tests. The additional information obtained from CPET/RHC was associated with significant therapeutic changes in 58% of subjects.

Findings from our study underscore the complexity of cardiopulmonary disease in patients with SSc. Significant ventilatory, pulmonary vascular, or left ventricular diastolic dysfunction limited exercise in 13/19 (68%) subjects. The

remaining subjects had abnormalities in exercise tolerance demonstrated by a low maximal VO₂ without clear evidence for an organ-specific etiology. Additionally, in about half of the subjects, either CPET or RHC identified significant additional abnormalities that were not felt to be exercise-limiting with combined analysis. For example, 2 subjects experienced mean PA pressures > 30 mm Hg during exercise, levels previously felt to indicate the presence of exercise-induced pulmonary hypertension¹⁶, but were not felt to be pulmonary vascular-limited by CPET findings. This is in concordance with recent guidelines suggesting that hemodynamic cutoffs alone are not sufficient to diagnose exercise-induced pulmonary vascular disease¹⁷.

Additionally, the utility of previously published CPET algorithms¹⁵ alone for the diagnosis of exercise limitation in this population of patients with SSc was limited. The VE/VCO₂ at anaerobic threshold and the vital capacity — 2 CPET algorithmic branch points potentially helpful in distinguishing between pulmonary vascular disease, LVDD, and nonpulmonary origin O₂ delivery deficit¹⁵ — did not differentiate diagnostic categories of exercise limitation in these SSc subjects. VE/VCO₂ as a measure of ventilatory efficiency may be elevated due to factors that increase pul-

monary dead space, including interstitial lung disease and chronic heart failure¹⁸, limiting its discriminative ability in this population with potentially both processes. Alternatively, the elevated VE/VCO₂ seen across diagnostic categories in this study (mean 40 ± 8.7) might suggest altered chemosensitivity¹⁹, perhaps as a result of SSc alone. Further studies might investigate this possibility of altered chemosensitivity in SSc. Vital capacity, like VE/VCO₂, was abnormal in the majority of these SSc subjects with varying degrees of interstitial lung disease, thus limiting its use in discriminating pulmonary vascular disease from LVDD. Only an elevated P(A-a)O₂ was able to discriminate a pulmonary vascular limitation from LVDD. Further studies might seek to evaluate the accuracy of an approach that combines exercise echocardiography and CPET with P(A-a)O₂ to discriminate the diagnosis of LVDD from pulmonary vascular disease in patients with SSc.

The lack of correlation between prior noninvasive testing and CPET/RHC results is notable. Ambulatory pulse oximetry and arterial blood gas testing performed during CPET testing were not correlated. This is likely secondary to a poor signal obtained from outpatient digital oximetry due to skin thickness²⁰ and resulted in the 50% false-positive rate for ambulatory oxygen desaturation in predicting an abnormal CPET A-a gradient. This high incidence of false-positive desaturation with digital pulse oximetry in SSc should be kept in mind and prompt use of alternative sites (e.g., ear-lobe) or confirmatory arterial blood gas testing in SSc patients with suspected hypoxemia.

Our study replicates results of studies by Steen, *et al*¹² and Hsu, *et al*¹³, which found that PASP estimated by resting echocardiography were not accurately predictive of exercise-induced pulmonary hypertension in subjects with SSc. Steen, *et al* showed that exercise echocardiography was more accurate (81%) than resting echocardiography in diagnosing exercise-induced elevations in pulmonary artery pressures, but it could not exclude diastolic dysfunction¹². Although patients with known diastolic dysfunction were excluded in the Steen study, both of our studies demonstrate a similar proportion (15%–21%) of LVDD as a cause of dyspnea in SSc patients. This finding of prevalent, occult LVDD lends support to the use of invasive hemodynamic monitoring with CPET to accurately discriminate between pulmonary venous and pulmonary arterial hypertension in SSc patients with undiagnosed dyspnea. The discrimination between these entities is critical for treatment decisions: SSc patients treated with pulmonary vasodilators for suspected PAH may develop significant pulmonary edema in the setting of occult LVDD²¹.

In contrast to the study of Steen, *et al*, we did not find that a low DLCO or elevated FVC%/DLCO% ratio reliably predicted a pulmonary vascular limitation to exercise. However, the median FVC%/DLCO% ratio for our subjects with PVL (1.8) was similar to that seen previously in SSc

subjects with exercise-induced elevations in PA pressures¹². Further studies with a greater number of subjects are warranted to validate FVC%/DLCO% as a potentially noninvasive predictor of pulmonary vascular exercise limitation in patients with SSc.

The chief limitation of our study is its retrospective design, which resulted in an absence of strict standardization for CPET/RHC diagnoses. However, a blinded investigator review of subject data demonstrated high concordance with the initial diagnostic impressions. Additionally, availability of complete data from retrospective chart review, such as anti-nuclear antibody patterns or a graded severity of interstitial lung disease, was limited. This additional data may have enhanced the predictive ability of noninvasive testing. The single-center referral basis of subject selection also may decrease the external validity of these findings. The small sample size may have limited the power to detect small differences between diagnostic groups. Information on longterm clinical outcomes related to the diagnoses obtained from CPET/RHC was not available and no comparable control group of dyspneic patients with SSc and no CPET/RHC testing was available, limiting evaluation of the clinical utility of CPET/RHC in these subjects. Finally, RHC is an invasive procedure with the potential for complications; CPET/RHC should be performed only at experienced centers in patients with suspected pulmonary vascular disease or LVDD.

Our study describes the etiology of exercise limitation in SSc patients referred for cardiopulmonary exercise testing with right-heart catheterization. We have shown that CPET/RHC may discriminate the etiology of dyspnea and exercise intolerance in selected SSc patients with nondiagnostic preliminary testing. Additionally, the study demonstrates the relatively high prevalence of pulmonary vascular disease and left ventricular diastolic dysfunction, undetected by resting echocardiography, as a cause of unexplained dyspnea on exertion in patients with SSc. Finally, CPET/RHC testing produced additional diagnostic information that contributed to treatment decisions in the majority of patients. Further study of CPET/RHC testing in SSc patients with potentially multifactorial dyspnea is recommended.

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APPENDIX Supplementary Table 1. Pulmonary function test data.

Measurement	Mean ± SD
FVC, l	2.46 ± 0.59
FVC, % predicted	71.5 ± 20.3
FEV ₁ , l	1.94 ± 0.46
FEV ₁ , % predicted	75.2 ± 19.4
FEV ₁ /FVC	0.79 ± 0.06
DLCO, ml/min/mm Hg	11.9 ± 3.76
DLCO, % predicted	54.4 ± 16.2
% FVC/% DLCO	1.43 ± 0.72

Supplementary Table 2. Complete cardiopulmonary exercise test data.

Measurement	Mean ± SD
Work, watts	86.9 ± 28.6
Work, % predicted	76.8 ± 29.1
VO _{2max} , l/min	1.12 ± 0.40
VO _{2max} , ml/min/kg	16.1 ± 4.21
VO _{2max} , l/min, % predicted	54.2 ± 17.9
AT, l/min	0.80 ± 0.32
AT % VO _{2max} predicted	37.5 ± 14.1
Resting SpO ₂ , %	97.3 ± 1.73
Peak exercise SpO ₂ , %	95.5 ± 2.71
SBP _{max} , mm Hg	169 ± 24.0
HRR, bpm	4.1 ± 16.3
O ₂ pulse, ml/beat	6.89 ± 2.29
O ₂ pulse, % predicted	62.3 ± 15.8
BR, %	22.0 ± 16.2
RR, bpm	47.6 ± 10.7
TV, l	1.27 ± 0.33
Vd/Vt, rest	0.39 ± 0.11
Vd/Vt, exercise	0.23 ± 0.08
P(A-a)O ₂ , rest, mm Hg	12.3 ± 10.9
P(A-a)O ₂ , exercise	25.1 ± 18.6
pH, rest	7.42 ± 0.03
PaO ₂ , rest, mm Hg	89.4 ± 13.6
PCO ₂ , rest, mm Hg	38.9 ± 4.45
HCO ₃ , rest, meQ/l	25.3 ± 4.25
pH, exercise	7.32 ± 0.04
PaO ₂ , exercise	92.7 ± 14.4
PCO ₂ , exercise	34.1 ± 7.06
HCO ₃ , exercise	17.1 ± 2.13
VE/VCO ₂	40.6 ± 8.91
etCO ₂ AT, mm Hg	35.9 ± 4.27
etCO ₂ /VE/VCO ₂	0.95 ± 0.28

with our patients during cardiopulmonary exercise testing and right-heart catheterization. We also appreciate the editorial input of Elizabeth Klings, MD, to this report.

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