Exercise Hemodynamics for the Diagnosis of Diastolic Dysfunction in Dyspneic Patients with Systemic Sclerosis

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ABSTRACT: **Background:** Previous studies have demonstrated the utility of exercise hemodynamics during right heart catheterization (RHC) in the diagnosis of diastolic dysfunction (DD). Little data exists regarding exercise hemodynamics during RHC in symptomatic systemic sclerosis (SSc) patients.

Objectives: To assess the added diagnostic value of using exercise hemodynamics during RHC in assessment of patients with symptomatic SSc.

Methods: We performed 22 RHCs in 17 SSc patients with dyspnea and/or pulmonary arterial hypertension (PAH). Exercise was performed in 15 RHCs using isotonic arm exercises while holding a 1 kg weight in each hand. Measurements of pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure (PAWP), and cardiac output (CO) were taken at rest and during peak exercise.

Results: Normal resting RHC (PAP 22 ± 3 mmHg, PAWP 11 ± 3 mmHg) was found in seven cases. Of these, exercise induced elevation in PAP was found in three (38 ± 7 mmHg), and exercise induced elevation in PAWP was found in four (24 ± 6 mmHg). Elevated resting PAP was found in 15 (41 ± 11 mmHg) with minor changes in exercise. Of the 22 RHCs, elevation of the PAWP was found in 11 (50%), half of which were in response to exercise.

Conclusions: In symptomatic SSc patients, exercise hemodynamics provides important information on diastolic dysfunction that is not available with non-invasive testing. Findings on exercise RHC can explain patient symptoms in up to 50% of cases. Earlier and more accurate diagnosis of patient symptoms can aid in tailoring the correct therapy for each.

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KEY WORDS: systemic sclerosis (SSc), pulmonary hypertension, diastolic dysfunction, right heart catheterization (RHC), exercise hemodynamics

Dyspnea is a common complaint in patients with systemic sclerosis (SSc) and can be secondary to interstitial lung disease, pulmonary vascular disease, and cardiac disease or a combination thereof [1]. It is often difficult to identify the exact cause or causes of the patient's symptoms. Previous studies have discussed the utility of right heart catheterization (RHC) in the diagnosis of pulmonary arterial hypertension (PAH) in patients with SSc [2-5]. However, few studies have addressed the issue of diastolic dysfunction as a cause of dyspnea in SSc [6,7]. In a previous study, we demonstrated the value of exercise RHC in unmasking diastolic dysfunction (DD) in patients with normal resting pulmonary artery pressures [8]. The aim of our current study is to describe the added diagnostic value of using RHC and exercise hemodynamics in the work-up of SSc patients presenting with dyspnea.

*The first and second authors contributed equally to this study

METHODS

The study comprised 17 consecutive patients (15 female) with an established diagnosis of SSc who underwent RHC at our center between 2004 and 2015. A total of 22 RHCs were performed on these patients during that time. Clinical data, including baseline characteristics, co-morbidities, laboratory data, medical treatment, and echocardiographic data were retrieved from the electronic patient records.

Two-dimensional and Doppler echocardiography was performed by using 3.5 MHz transducers. Studies were then digitally filed (McKesson's Horizon Cardiology™ Medical Software; Tel Aviv, Israel). Echocardiograms were performed within 1 month of the index RHC. All echocardiograms were interpreted by two independent echocardiographers in accordance with the American Society of Echocardiography (ASE) Guidelines and Standards [9]. Left ventricular ejection function was calculated by the modified Simpson's method.

Diastolic function as defined by ASE:

- Grade I: E/A ratio < 0.8 with a deceleration time >200 ms, E/e' < 8
- Grade II: E/A between 0.8–1.5 and deceleration time between 160–200, E/e' 9-12
- Grade III: E/A > 1.9, deceleration time < 160, E/e' > 13.

Systolic PAP was calculated using the tricuspid valve jet's peak velocity minus the systolic right atrial pressure. An elevated systolic PAP is considered elevated if over 40 mmHg [9].

Table 1. Baseline characteristics

Characteristic	Number
Age, years	39 ± 16
Gender, female	15 (88%)
Smoking	3 (18%)
Body mass index	27 ± 5
Dyslipedemia	6 (35%)
Diabetes mellitus	1 (0.6%)
Hypertension	10 (58%)
Atrial fibrillation	3 (18%)
Treatment with diuretics	10 (58%)
Chronic obstructive pulmonary disease	3 (18%)
6 minute walk test	305 ± 130
Interstitial lung disease	5 (29%)

Table 2. Hemodynamic data

Patient	PAP		PAWP		TPG		CO		PVR	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Group 1: Elevated resting PAP	26	23	17	28	9	-5	5.8	–	2	–
	27	32	11	29	16	3	6.5	9.0	2.5	0.3
	32	50	17	26	15	24	3.1	6.5	4.8	3.7
	32	38	18	21	14	17	2.6	5.6	5.5	3.2
	35	30	16	18	19	12	6.0	7.4	3.3	1.6
	37	46	28	32	9	14	5.4	–	1.7	–
	39	–	18	–	21	–	2.9	–	5.6	–
	39	–	7	–	32	–	3.4	–	9.3	–
	40	–	10	–	30	–	2.2	–	13.5	–
	41	–	7	–	34	–	3.2	–	10.7	–
	46	46	0	5	46	41	2.4	2.8	18.9	14.6
	47	62	11	18	36	44	3.3	6.6	10.9	6.7
	50	–	11	–	39	–	2.4	–	16.4	–
	51	57	7	6	44	51	2.0	2.2	21.5	22.9
	69	–	6	–	63	–	2.2	–	28.1	–
	17	11	10	3	7	8	6.4	8.8	1.1	0.9
Group 2: Normal resting PAP	21	22	15	16	6	6	5.6	7.1	1.1	0.8
	22	27	7	14	15	13	5.2	7.5	2.9	1.7
	23	31	10	25	13	6	5.3	4.8	2.5	1.2
	23	45	9	25	14	20	2.6	5.6	5.4	3.6
	24	39	13	31	11	8	3.8	5.5	2.9	1.5
	25	–	15	–	10	–	3.6	–	3.0	–
Average	35 ± 13	37 ± 14	12 ± 6	20 ± 9	23 ± 15	17 ± 16	4 ± 1	6 ± 2	8 ± 7	5 ± 7

CO = cardiac output, PAP = pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure, PVR = pulmonary vascular resistance (Wood's units), TPG = trans-pulmonary gradient

Right heart catheterization was performed via femoral venous puncture in all patients by the Seldinger technique with a 7.5 French Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA). All patients had resting baseline measurements recorded, including heart rate, pulmonary arterial pressure (PAP), and capillary wedge pressure (PAWP) measured at the midaxillary line. Measurements were made by averaging the mean pressure of three cardiac cycles during end expirium. Cardiac output (CO) was calculated using estimated Fick and/or thermal-dilution methods. The stroke volume was then calculated from the CO divided by the heart rate. The trans-pulmonary gradient (calculated by subtracting the mean PAWP from the mean PAP), diastolic pulmonary gradient (calculated by subtracting the PAWP from the diastolic PAP), and pulmonary vascular resistance (defined as the trans-pulmonary gradient divided by the cardiac output) were calculated. Normal resting PAP was defined as PAP below 25 mmHg and pulmonary capillary wedge pressure (PAWP) below 15 mmHg.

Exercise hemodynamics were performed in 15 of the RHCs. Exercise was performed in a similar fashion for all patients and consisted of isotonic arm exercises while holding a 1 kg weight in each hand. Measurements were performed during peak exercise and before cessation of activity if possible. Exercise was terminated if the patient could not continue or if the pulse rate increased by at least 20% above baseline. Cardiac output was measured using the thermal technique in patients performing exercise. Exercise pulmonary arterial hypertension was defined as a PAP > 30 mmHg and DD as a PAWP > 15 mmHg [2,5].

RESULTS

Data are presented as frequencies or means ± standard deviation.

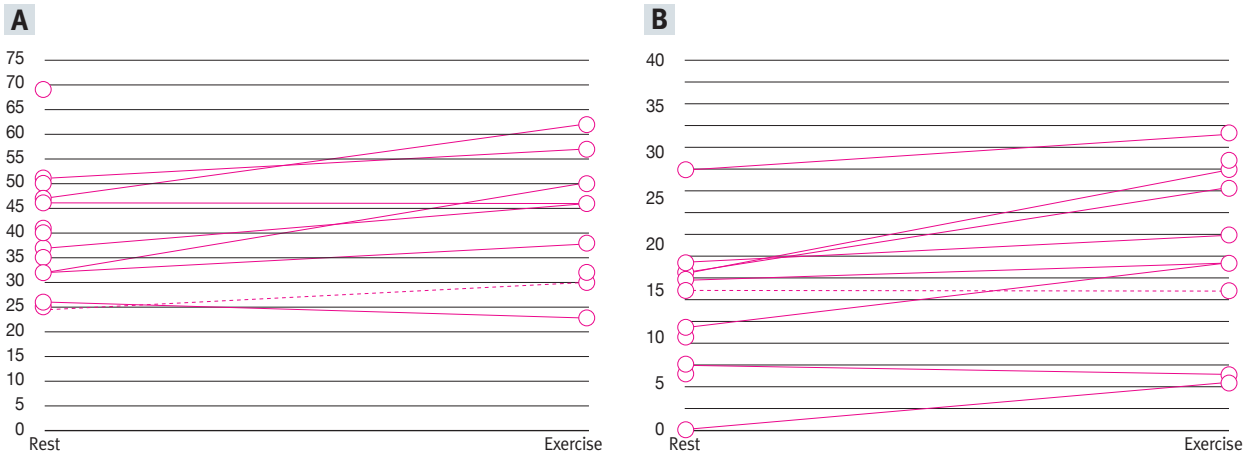
We performed 22 RHCs in 17 patients with SSc. Informed, written consent was obtained from each patient. The initial indication for catheterization was for assessment of suspected PAH in 10 patients, and unexplained worsening of dyspnea in 12 patients with an established diagnosis of PAH. Repeated RHCs were performed in four patients due to worsening symptoms. Baseline characteristics are presented in Table 1. Notably, relatively few patients had diabetes, whereas hypertension was present in 56% of this young (39 ± 16 years of age) cohort of predominantly female patients.

The 22 RHCs were grouped into those with elevated resting PAP (group 1) and those with normal resting PAP (group 2) [Table 2]:

Group 1 (elevated resting PAP) included 15 cases (41 ± 11 mmHg). Resting PAWP was normal in nine of these cases (8 ± 4 mmHg), whereas elevated resting PAWP was found in six cases (19 ± 4 mmHg). Exercise was performed in nine cases from group 1. Minor changes in PAP were noted on exercise [Figure 1A]. In addition, two cases had elevated PAWP on exercise [Figure 1B].

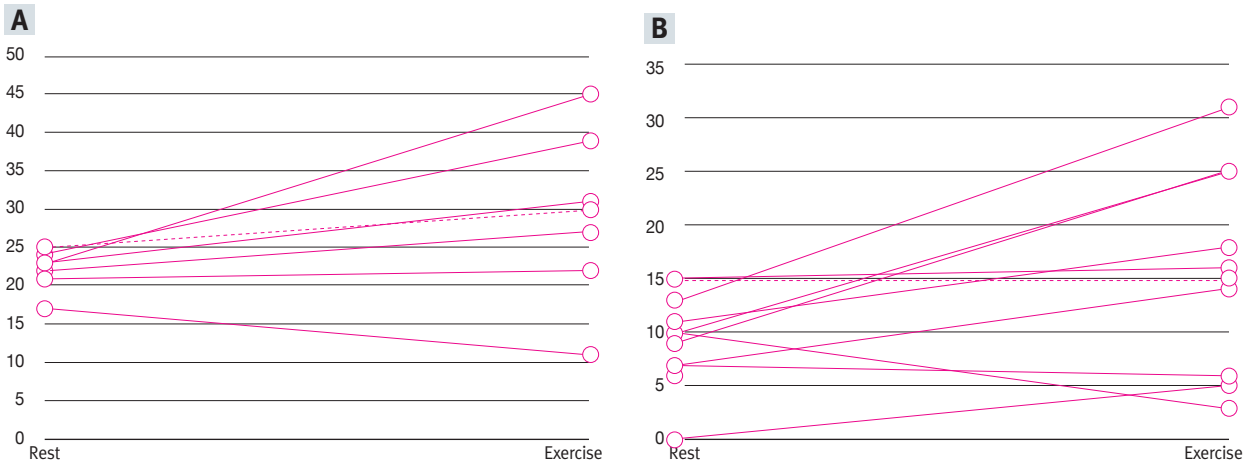
Group 2 (normal resting PAP) included seven cases (22 ± 3 mmHg). In all these cases the resting PAWP was normal (11 ± 3 mmHg). Exercise was performed in six cases. Exercise induced elevation in PAP was found in three cases (38 ± 7 mmHg), whereas exercise induced elevation in PAWP was found in four cases (24 ± 6 mmHg) [Figure 2A and 2B].

Figure 1. Exercise hemodynamics in group 1 (patients with elevated resting PAP). **[A]** Exercise PAP **[B]** Exercise PAWP



Dotted line represents upper limit of normal PAP or PAWP, respectively
PAP = pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure

Figure 2. Exercise hemodynamics in group 2 (patients with normal resting PAP). **[A]** Exercise PAP **[B]** Exercise PAWP



Dotted line represents upper limit of normal PAP or PAWP, respectively
PAP = pulmonary arterial pressure, PAWP = pulmonary arterial wedge pressure

Overall, evidence of diastolic dysfunction, as assessed by PAWP of greater than 15 mmHg, was found in 11 cases (50%), half of these were revealed by exercise hemodynamics [Figure 2B].

All patients demonstrated normal left ventricular volumes with normal left ventricular systolic function. Estimated pulmonary arterial systolic pressure was elevated in 13 patients (76%). Diastolic function was normal in five patients and not assessable in another five patients. Measures of DD were present in six patients (Grade I DD in three patients and Grade II DD in three patients). Only two of the six patients with DD established on echocardiography showed elevated filling pressures on RHC. None of the six patients with elevated filling pressures found on exercise RHC showed signs of DD on echocardiography. Of the five patients in which we could not assess diastolic function, four patients had elevated filling pressures on exercise RHC.

DISCUSSION

We assessed exercise hemodynamics in patients with SSc. The major findings of our study are that diastolic dysfunction is common in patients with SSc, and that exercise hemodynamics unmasks this increased filling pressure in a significant proportion of patients with otherwise normal PAWPs, regardless of their resting PAP.

It is increasingly evident that myocardial involvement is common in patients with SSc. Fernandes and co-authors [10] found evidence of myocardial fibrosis in 94% of asymptomatic patients undergoing myocardial biopsy. Recent advances in cardiac magnetic imaging (cMR) have enabled relatively easy, non-invasive assessment of myocardial disease. Indeed, recent cMR studies have shown almost universal myocardial involvement approaching that found on autopsy [11,12]. However, the fibrosis found on cMR did not correlate with the level of diastolic dysfunction, explained by the diffuse and patchy of fibrosis in these patients [12]. Also, early interstitial remodeling may be detected on cMR before the appearance of symptoms and overt DD [13,14].

Echocardiography is currently the most common tool used for the assessment of both systolic and diastolic left ventricular function. Ciurzynski et al. [15] demonstrated that 34% of SSc patients had evidence DD on echocardiography. D'Alto and colleagues [11] showed impaired left ventricular filling in a significant proportion of 74 SSc patients when compared to 71 age/gender/weight/body surface area-matched controls assessed by inverted E/A ratio on the standard echocardiogram (45% vs. 27% respectively, $P = 0.007$). Furthermore, Maione and co-authors [16] showed an increasing prevalence of DD over time with a prevalence of 30% at study onset and increasing to 38% at the end of a 6–12 year follow-up period.

Right heart catheterization is mandatory for the assessment of pulmonary hypertension. Classically, resting hemodynamic values from RHC have been used to verify pulmonary hypertension, and classify it as either pre-capillary (arterial) or post-capillary (venous). We recently reported on our experience with exercise hemodynamics during RHC for the assessment of patients with pulmonary hypertension [8]. We demonstrated that exercise hemodynamics unmasked early DD in a significant proportion of the study population, suggesting a reclassification of patients from pre-capillary to post-capillary etiology. In our current study, we assessed exercise hemodynamics in 22 RHCs in a cohort of 17 symptomatic SSc patients. We found that a full 50% of these patients undergoing RHC had DD. Pure PAH was found in nine RHCs without signs of DD. Exercise hemodynamics were performed in 15 RHCs and unmasked DD in 8 of these cases. Notably, four patients with completely normal resting right heart pressures had evidence of DD on exercise. Another two patients with PAH also had evidence of exercise DD possibly complicating the pre-existing PAH. Progression of left ventricular DD was seen in three of the patients who underwent serial RHCs, with increasing PAWP demonstrated on successive catheterizations.

While RHC is widely used to assess pulmonary hypertension in SSc patients, few studies have shown the added diagnostic value of using exercise hemodynamics in RHC in patients with SSc. Hager et al. [6] examined exercise hemodynamics during RHC in asymptomatic SSc patients. All of these patients had normal resting hemodynamics with elevated exercise PAP on echocardiography. Similar to our study, 27% of these patients developed an elevated PAWP on exercise. Unlike Hager, our cohort was a highly selective group of SSc patients who were referred to RHC due to symptoms of dyspnea or PAH. We demonstrated that in a significant proportion these patients DD was either responsible for, or contributed toward, these patients' symptoms. In fact, exercise hemodynamics was instrumental in understanding the patient's pathology in 50% of RHCs performed. Furthermore, serial RHCs were able to show the progression of disease from normal, through subclinical and to abnormal values over time.

Exercise echocardiography in SSc patients has been assessed previously [17,18]. Ciurzynski and colleagues [7] found evidence of exercise induced PAH attributed to DD on echocardiography. They verified these findings on RHC as a subgroup of 20 of these patients. Assessment of DD on echocardiography is not straight forward [18,19]. Indeed, resting echocardiography performed on our patients was unreliable in predicating DD demonstrated on RHC.

LIMITATIONS

Our retrospective study included all SSc patients referred for RHC during the study period. As such, it is obviously biased toward patients with more severe symptoms, and therefore we cannot deduce the prevalence of DD in asymptomatic or less symptomatic patients who were not referred for RHC. The effects of hypertension, a common cause of diastolic dysfunction and present in almost 60% of patients in our series, cannot be differentiated from the direct effects of SSc on the myocardium. Echocardiograms were performed within 1 month of the index RHC and not necessarily at the same time as the RHC, which could influence findings due to different filling conditions at different time points. However, in a real world setting, this is precisely the data available to the treating physician who must decide whether invasive RHC may aid in the diagnosis and management of the patient. Unfortunately, while of great interest, stress echocardiograms were not available for comparison in the majority of subjects. Notwithstanding, the strength of our study lies in its novel approach in "real-world" patients, utilizing exercise hemodynamics to unmask occult DD, which is present in a significant proportion of these symptomatic patients

CONCLUSIONS

In symptomatic SSc patients, exercise hemodynamics provides important information on diastolic dysfunction that is not present on routine non-invasive testing. Findings on exercise RHC can explain the patient's symptoms in up to 50% of cases. Earlier and more accurate diagnosis of patients' symptoms can aid in tailoring the correct therapy for each patient.

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Capsule

Kinase networks in inflammation

Although inflammation in rheumatoid arthritis is driven by the increased activity of p38, inhibitors of this kinase are ineffective in patients. Using synovial fibroblasts and fluid from rheumatoid arthritis patients, **Jones** et al. found that p38 mediated negative cross-talk to the related kinase JNK. Thus, inhibiting p38 facilitated JNK activity and the perpetuation of inflammatory cytokine production. Inhibitors of the upstream kinase TAK1 curbed the activity of both the p38 and JNK pathways in synovial fibroblasts cells. Such inhibitors might thus be effective in treating rheumatoid arthritis.

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Capsule

Pain and mortality in older adults: the influence of pain phenotype

Moderate to severe chronic pain affects 1 in 5 adults. Pain may increase the risk of mortality, but the relationship is unclear. **Smith** et al. investigated whether mortality risk was influenced by pain phenotype orcharacterized by pain extent or pain impact on daily life. The study population was drawn from two large population cohorts of adults ages ≥ 50 years, the English Longitudinal Study of Ageing (n=6324) and the North Staffordshire Osteoarthritis Project (n=10,985). After adjustments, the report of any pain, mortality rate ratio (MRR) 1.06, 95% confidence interval (95%CI) 0.95–1.19, having widespread pain, American College of Rheumatology criteria 1.07, 95%CI 0.92–1.23 or Manchester 1.16, 95%CI 0.99–1.36, was not associated with an increased risk of mortality. Participants who were often troubled with pain, MRR 1.29, 95%CI 1.12–1.49, and those who reported quite a bit of pain interference, MRR 1.38, 95%CI 1.20–1.59, and extreme pain interference, MRR 1.88, 95%CI 1.54–2.29, had an increased risk of all-cause mortality.

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