Prevalence of Exercise Pulmonary Arterial Hypertension in Scleroderma

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ABSTRACT. ***Objective***. Pulmonary arterial hypertension (PAH) is a complication of scleroderma (systemic sclerosis, SSc); as soon as PAH develops, the patient's prognosis deteriorates rapidly. Early detection of PAH ensures timely treatment. We investigated the prevalence of exercise-induced PAH in a cohort of patients with SSc, and examined the relation between exercise-induced PAH and clinical characteristics and biochemical markers.

Methods. Patients with SSc and normal resting systolic pulmonary arterial pressure (sPAP) were studied. Eligible patients were asked to perform cycloergometer exercise until exhaustion, and exercise sPAP was measured. All patients had their pulmonary function tested and underwent echocardiography at rest. Brain natriuretic peptide (BNP) was also determined.

Results. Forty-one patients with SSc were studied. Mean sPAP at rest was 29.7 mm Hg, rising to a mean of 41.4 mm Hg on exercise. Eleven of 41 patients (26.8%) had sPAP post-exercise > 50 mm Hg and 8/41 (19.5%) > 55 mm Hg. A significant correlation was found between exercise sPAP and DLCO ($p = 0.008$) and between sPAP and BNP levels ($p = 0.04$). Pre-existing severe Raynaud's phenomenon was more prevalent (50% vs 20%), DLCO levels lower (78.9 vs 92.7 % predicted), and BNP levels higher (72.6 vs 42.1 pmol/ml) in patients with exercise sPAP > 55 mm Hg.

Conclusion. The prevalence of exercise-induced PAH in patients with scleroderma is high. Patients with lower DLCO and higher levels of BNP are at higher risk of developing higher sPAP. Studies with longterm followup are required to evaluate the risk of developing resting PAH in these patients. (First Release July 15 2008; J Rheumatol 2008;35:1812–6)

Key Indexing Terms:
PULMONARY ARTERIAL HYPERTENSION PROGNOSIS SYSTEMIC SCLEROSIS
PULMONARY ARTERIAL SYSTOLIC PRESSURE EARLY DETECTION

Pulmonary arterial hypertension (PAH) is a disease of the pulmonary vasculature, characterized by a progressive increase in pulmonary vascular resistance, which leads eventually to right ventricular failure and death. PAH is a major complication of autoimmune conditions, particularly scleroderma (systemic sclerosis, SSc)[1]. The prevalence of PAH in patients with SSc ranges from 12% to 26%, depending on the diagnostic criteria, diagnostic methods, and sample population[2,3]. Once PAH develops the prognosis deteriorates, with 1-year survival in SSc patients decreasing from over 90% to 55% to 68%[4-6]. Thus, PAH is one of the main causes of morbidity and mortality in patients with SSc. It is therefore essential to develop methods and identify clinical or analytical factors that will allow early detection of PAH in patients with SSc and make earlier intervention more likely. Although right heart catheterization (RHC) is required for a definitive diagnosis of PAH, Doppler echocardiography has been widely adopted in recent years as an initial screening technique, thanks to its good correlation with the hemodynamic values measured with RHC[7].

PAH is defined as a mean pulmonary arterial pressure (PAP) ≥ 25 mm Hg when resting or ≥ 30 mm Hg with exercise on right heart catheterization[8]. This means that patients may, at least initially, have PAH during exercise without it being evident at rest. It is important to acknowledge that the natural evolution of and secondary risks associated with development of SSc-related PAH are not well known. Chang, *et al* reported that among 361 patients without evidence of PAH on first echocardiography, 92 (25.5%) developed mild to moderate PAH and 49 (13.6%) developed severe PAH. Further, 17.7% of the patients with mild to moderate PAH progressed to severe PAH after 3.2 years of

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followup[9]. It is possible that in an initial phase, PAH will only become manifest during exercise. Thus, an excessive increase of systolic PAP (sPAP) when exercising, measured by Doppler echocardiography, would be associated with decreased pulmonary vasodilator reserve and could be a valuable early marker of subclinical vascular damage.

We assessed pulmonary pressure response to exercise using Doppler echocardiography in patients with SSc, evaluating the prevalence of exercise-induced PAH. As secondary objectives we analyzed clinical factors predictive of PAH during exercise and evaluated the correlation between exercise sPAP and brain natriuretic peptide (BNP) levels[10,11] and exercise sPAP and diffusing capacity for carbon monoxide (DLCO)[12,13].

MATERIALS AND METHODS

Study design. This was a cross-sectional survey, carried out at the Systemic Autoimmune Diseases Unit and the Cardiology Department of the Hospital Clínico San Cecilio in Granada, Spain. The study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee, Comité Ético del Hospital Universitario San Cecilio. Informed, written consent was obtained from all participating patients.

Patient population. Patients were included in the study if they met the American College of Rheumatology (ACR) diagnosis criteria for SSc[14] and had not been previously diagnosed with PAH (resting sPAP < 35 mm Hg). Patients were excluded from the study if they had a known cardiovascular disease or confirmed PAH or if they had other diseases associated with development of PAH. Patients were also excluded if they had taken prostanoids, sildenafil, or bosentan within the previous 3 months. Female patients could not be pregnant.

Study assessments. Pulmonary function tests (PFT), including total lung capacity (TLC) and DLCO, were performed in every patient. Thoracic high-resolution computed tomography (HRCT) was performed in those patients with a TLC < 70% predicted or a DLCO < 80% predicted to exclude interstitial lung disease[15]. Patients with a TLC < 60% of predicted were excluded and also those with a TLC between 60% and 70% and significant fibrosis on HRCT. Raynaud's phenomenon (RP) was considered severe if digital ulceration was present.

All patients underwent echocardiography at rest. Echocardiographic measurements were obtained through a Doppler bidimensional echocardiograph with second harmonic imaging (Vivid 7 Dimension; General Electric Co.). All echocardiographic assessments were performed by the same experienced operator to avoid interindividual variability.

The sPAP was calculated through maximum speed of tricuspid insufficiency according to common practice (sPAP = 4 $vmax^2$ + right atrial pressure)[16]. If needed, intravenous shaken saline was administered to enhance the Doppler signal of tricuspid insufficiency. Right atrial pressure was estimated in all cases at 5 mm Hg.

Patients performed cycloergometer exercise using a WHO protocol. The protocol started with an initial workload of 25 W, followed by progressive increases of 25 W every 2 minutes (level I to IV[17]). Patients exercised until they could go no further. Blood pressure was measured with arm sphygmomanometer and heart rate was monitored continuously via electrocardiography (ECG). Echocardiography sPAP measurement was performed immediately post-exercise using methods identical to those used for baseline measurements.

Blood samples were taken to determine baseline BNP levels[10].

Data analysis. Data are given as mean ± SD values. Fisher's exact test was used for comparisons of the discrete measures between different subgroups. Correlations between sPAP and DLCO and sPAP and BNP were assessed measuring Pearson correlation coefficient. A probability value of $p < 0.05$ was considered significant. A receiver-operating curve (ROC) analysis was conducted to obtain a cutoff level of DLCO and BNP for the classification of subjects with and without PAH at exercise, calculating the respective areas under the curve. Data analysis was performed using statistical software (SPSS, version 13.0).

RESULTS

Forty-eight patients with SSc were recruited in the study, of whom 7 were excluded owing to the absence of tricuspid regurgitation at rest or during exercise. Therefore the final study population was 41 patients: 30 with limited cutaneous systemic sclerosis (lcSSc) and 11 with diffuse cutaneous systemic sclerosis (dcSSc). The clinical and demographic profile of the patients is presented in Table 1.

All individuals exercised until exhaustion, reaching 85% of their theoretical maximum heartbeat rate. A level III of exercise was reached in 46.5% of patients and level IV in 24.2%, respectively. Mean sPAP was 29.7 ± 5.3 (21–35) mm Hg at rest and 41.2 ± 12.8 (25–80) mm Hg during exercise. At rest, all echocardiographic variables were in the normal range. Figure 1 shows the percentage of patients with exercise sPAP > 50 mm Hg; during exercise sPAP was > 55 mm Hg in 11 patients (19.5%) and > 60 mm Hg in 4 patients (9.8%). The mean increase in pressure detected in the total patient population was 16.7 ± 9.8 (5–50) mm Hg.

When a possible link between peak sPAP during exercise and other variables obtained in the study was investigated, a significant negative correlation with DLCO (r = –0.4, p =

Table 1. Baseline patient demographics.

Characteristic	n = 41
Age, yrs, mean ± SD	53.4 ± 12.4
Time since diagnosis, mo, mean ± SD	15.7 ± 11.6
Interstitial involvement, %	10
DLCO (% predicted), mean ± SD	90.1 ± 19.9
TLC (% predicted), mean ± SD	102.9 ± 11.9
BNP, pmol/ml, mean ± SD	48.1 ± 39.5

DLCO: diffusing capacity for carbon monoxide; TLC: total lung capacity; BNP: brain natriuretic peptide.

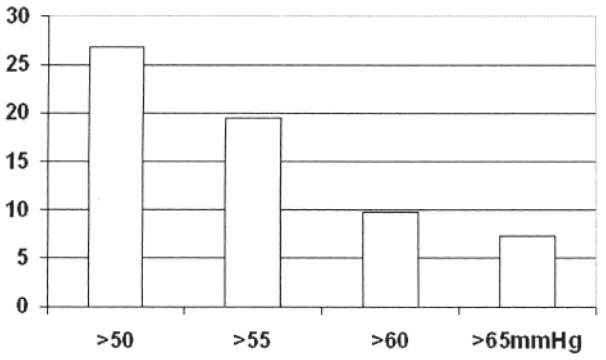

Figure 1. Prevalence of sPAP (mm Hg) during exercise using different cutoff.

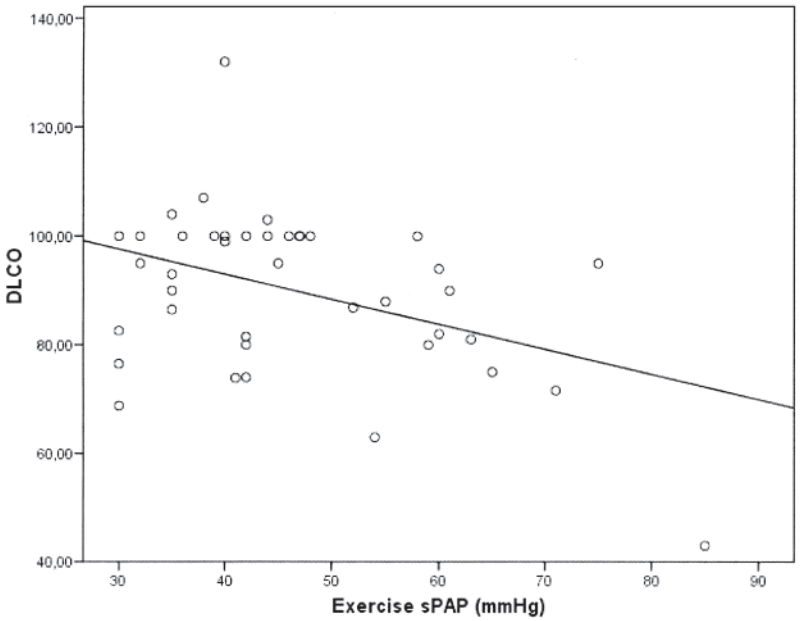

Figure 2. Correlation between sPAP (mm Hg) and DLCO (% predicted); r = –0.4, p = 0.008.

0.008; Figure 2) and a positive correlation with BNP levels (r = 0.31, p = 0.04; Figure 3) were found. In patients with exercise sPAP > 55 mm Hg, DLCO levels were significantly lower (78.9 vs 92.7% predicted; p = 0.03) and BNP levels were significantly higher (72.6 vs 42.1 pmol/ml; p < 0.05). ROC analysis was performed, and the DLCO cutoff level that achieved the highest balance between sensitivity and specificity was 72% of predicted (sensitivity 79.9%, specificity 76.3%) using a sPAP > 55 mm Hg as threshold for the definition of exercise PAH. The prevalence of pre-existing severe RP was significantly higher in these patients (50% vs 20%; p < 0.05).

DISCUSSION

We observed elevation of sPAP to > 55 mm Hg during exercise in a high percentage of patients with SSc (19.5%), and 4 patients (9.8%) had sPAP > 60 mm Hg during exercise; all these subjects had sPAP < 35 mm Hg at rest.

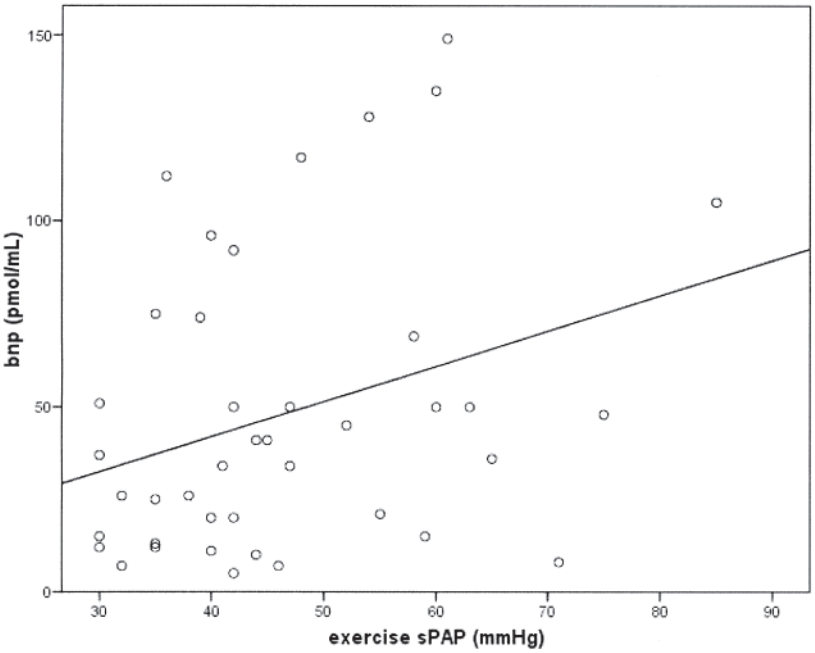

Figure 3. Correlation betwwen sPAP (mm Hg) and BNP (pmol/ml); r = 0.31, p = 0.04.

There are 2 studies of individuals with exercise-PAH associated with SSc. Alkotob, *et al*[18] demonstrated an increase to > 40 mm Hg in 46% of patients with SSc and observed that peak sPAP was linearly related to exercise time and maximum workload achieved. Similarly, Collins, *et al* observed that > 50% of patients with SSc presented an increase > 35 mm Hg with exercise[19]. These results are very similar to ours.

The exact mechanisms of increased sPAP during exercise are unknown. However, they are likely to be due, at least in part, to the early stages of endothelial dysfunction and vascular remodeling that may have little initial effect at rest but become more apparent during exercise. By comparison, in healthy individuals, sPAP does not exceed 40 mm Hg with exercise, except for athletes[20]. The echocardiographic variables of left ventricular function were normal both at rest and with exercise, and no data of systolic or diastolic left ventricular dysfunction were observed. Thus we think it unlikely that our patients had pulmonary venous hypertension.

We observed a significant correlation between DLCO and stress sPAP, and in ROC analysis a DLCO cutoff of 72% provided optimum discrimination for PAH at exercise. A retrospective case-matched controlled study showed a correlation between a progressive deterioration in DLCO and subsequent development of isolated PAH[12]. Recently, Allanore, *et al*[13] reported that the sensitivity and specificity of a DLCO/alveolar volume < 70% were 87.5% and 79.5%, respectively, in predicting PAH. Our results suggest that in patients with SSc who have low DLCO and normal sPAP at rest, exercise echocardiography could be useful in the early diagnosis of PAH.

Another factor significantly correlated with an exercise sPAP > 55 mm Hg was a preceding diagnosis of severe Raynaud's phenomenon. Patients with PAH frequently have severe peripheral vascular disease, functionally apparent as severe RP accompanied by digital ulceration[12]. In other autoimmune diseases such as systemic lupus erythematosus, RP is also correlated with elevated sPAP[21]. Several pathological mechanisms have been considered responsible for this association.

There is growing evidence that BNP level might be a biomarker for PAH in terms of screening, diagnostic evaluation, evaluation of response to therapy, and prediction of disease severity[10,11]. The relationship of BNP with exercise-induced PAH is uncertain. Our results suggest that BNP could prove useful as an objective, noninvasive means of identifying patients with exercise-induced PAH as a reflection of cardiac wall stress.

PAH is a serious and frequent complication in patients with SSc[2-6]. Early detection and treatment of this complication is necessary to improve prognosis. In most patients, the initial clinical presentation is dyspnea when exercising, often in the absence of abnormal sPAP at rest. The behavior of sPAP during exercise in patients with SSc is not well characterized. An excessive increase in sPAP with exercise could be the result of a decrease in the vasodilator reserve and may have a role as an early marker of subclinical vascular damage. Indeed, the relationship between DLCO and BNP with sPAP found in our study suggests that the presence of exertional PAH in SSc patients may actually be a marker of early vascular damage at pulmonary level in these patients.

Our study has several limitations: echocardiography during exercise is a nonstandardized method for the assessment of PAH, and exertional catheterization was not performed. A further limitation may be the small patient population, thereby possibly lacking statistical power to show significant differences compared with a larger sample. Similarly, followup was not long enough to allow us to assess whether patients with exercise-induced PAH are more likely to develop resting PAH in the future. Other factors including intraobserver variability and methodological and technical factors can also influence results; in our study, this was minimized by using a single operator for all measurements.

Our results show that prevalence of exercise PAH is high in patients with scleroderma. Those patients with elevated BNP or low DLCO are at a higher risk of exertional PAH, irrespective of normal Doppler echocardiography at rest. Detection of increased sPAP with exercise in patients with SSc and dyspnea could reveal the underlying cause of these symptoms. This finding could also help to identify those at a higher risk of developing severe PAH at a later stage. The natural history of these patients is unknown, making followup essential.

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