Risk Factors Associated with Pulmonary Arterial Hypertension in Colombian Patients with Systemic Sclerosis: Review of the Literature

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ABSTRACT. ***Objective.*** Considering the significant morbidity and mortality of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc) and the lack of precise information on disease in Latin America, we investigated the clinical and laboratory characteristics associated with PAH in Colombian patients with SSc and review the literature.

Methods. This multicenter study included patients followed at 5 rheumatology units that were systematically assessed using a pretested questionnaire on clinical and immunological variables, focusing on PAH. Conditional logistic regression was employed to assess association between PAH and specific clinical characteristics. A systematic review of the literature was performed through electronic databases.

Results. Of a total of 349 patients with SSc, 61 (17%) met the criteria for PAH. Pulmonary fibrosis [adjusted odds ratio (AOR) 7.37, 95% CI 3.67–14.81, $p < 0.0001$], microstomia (AOR 3.3, 95% CI 1.70–6.28, $p < 0.0001$), gastroesophageal reflux (AOR 2.41, 95% CI 1.31–4.43, $p = 0.005$), dysphagia (AOR 2.7, 95% CI 1.49–4.77, $p = 0.001$), hyperpigmentation (AOR 2.15, 95% CI 1.11–4.16, $p = 0.02$), and hypopigmentation (AOR 2.4, 95% CI 1.26–4.64, $p = 0.008$) were the most prevalent clinical characteristics associated with PAH, while anemia (AOR 5.4, 95% CI 1.98–14.93, $p = 0.001$) was observed as the unique laboratory risk factor. Association between subtypes of SSc and PAH was not observed. Significant differences in both clinical and laboratory data were observed among different series.

Conclusion. PAH may be a frequent complication of SSc in the Colombian population regardless of disease subtype. The identified clinical and laboratory risk factors might assist earlier diagnosis and guide decisions on therapeutic interventions on this critical complication of SSc. The reasons underlying the reported divergences among patients from different ethnicities are not fully understood, but it is most likely that both genetic and environmental factors are responsible for them. (First Release Jan 15 2008; J Rheumatol 2008;35:244–50)

Key Indexing Terms:
SYSTEMIC SCLEROSIS PULMONARY ARTERIAL HYPERTENSION COLOMBIA

Systemic sclerosis (SSc) is an unusual systemic autoimmune disease characterized by microvasculopathy with destruction or functional damage of small blood vessels, fibroblast activation, and excessive production of collagen. SSc is clinically characterized by different degrees of skin fibrosis and visceral organ involvement and the presence of specific autoantibodies in more than 95% of patients[1].

The epidemiology of SSc is not definitively established

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due to the relative rarity of the disease, the difficulty in diagnosing it, and its extreme clinical variability. SSc is found predominantly in women, with a peak of incidence between 45 and 64 years of age. There seems to be a higher frequency of the disease in Blacks, particularly in Black females[2]. Its prevalence is estimated to be 276 cases per million adults, with an annual incidence of 19.3 new cases per million adults each year[3].

The etiology of SSc is unknown, although the disease appears to be the result of a multifactorial process, including immune system alterations and genetic and environmental factors. Vascular injury is frequently the earliest manifestation of disease, while immune abnormalities, in particular serum autoantibodies, may also occur early in the course of SSc. Fibrosis, characterized by an excessive accumulation of collagen and extracellular matrix components, is usually a late feature[4].

Two clinical hallmarks of SSc are its clinical heterogeneity and the wide range of vascular and fibrotic manifestations, including organ involvement, which is why the different patterns and severity of internal organ manifestations are the most significant determinants of outcome[5,6]. The skin, lungs, gastrointestinal system, heart, and kidneys are the most frequent SSc targets. Pulmonary disease is a leading cause of death for patients with SSc[7] and, of the 2000 patients in the Pittsburgh scleroderma databank, of 211 patients who died of lung disease over the past 20 years, 113 died from isolated pulmonary arterial hypertension (PAH)[8]. Pulmonary manifestations of SSc include PAH and pulmonary fibrosis, which differ in their pathogenesis, clinical associations, predictive factors, and treatment[9]. PAH is considered the "bête noire" of systemic diseases, particularly in SSc, since it has a significant effect on quality of life, medical costs, and mortality[10]. The prevalence of PAH in patients with SSc might vary depending upon both the criteria and the method used for its diagnosis. By cardiac catheterization, the prevalence of PAH appears to be 12% when patients with interstitial lung disease[11] are included, compared to 7.85% when the analysis is limited to patients with only PAH[12]. Using echocardiogram, the diagnosis of PAH in SSc is estimated at 13.3%[13]. Nevertheless, the true incidence of PAH in SSc patients is underestimated due to the extremely low sensitivity of routine clinical tests[14].

PAH is a vasculopathy of the pulmonary vessels that is historically considered to occur mainly in patients with long-standing limited SSc who test positive for anticentromere antibodies (ACA)[15]. It has a major impact on survival and outcome, with a median survival of 50% at 12 months[5]. Survival rate, however, depends upon the severity of PAH at diagnosis[5].

Considering the high morbidity and mortality that PAH causes for SSc patients and the lack of precise information about the disease in Latin America, this study was done to determine the clinical and laboratory characteristics associated with PAH in Colombian patients.

MATERIALS AND METHODS

Study design and patients. This multicenter, cross-sectional study followed patients being assessed at 5 rheumatology units in Colombia. Information on patient demographics and cumulative clinical and laboratory manifestations over the course of the disease was obtained either by verification during discussion with the patient or by chart review. Data were collected with a specifically created standard data collection form. A guide to the data collection form was made to assure its reproducibility ($k > 0.7$). Each clinical and laboratory variable was registered as "present" or "absent" for each patient both at diagnosis and at any subsequent time during the course of the disease. All patients fulfilled the preliminary criteria for the classification of SSc established by the American College of Rheumatology[16].

Patients were classified as having either diffuse SSc or limited SSc, depending on the extent of skin involvement based on the criteria proposed by LeRoy, *et al*[1]. Age and sex were reported, and age at disease onset was considered to be the age at which the first signs and symptoms compatible with the disease appeared.

Diagnosis of PAH was confirmed by echocardiogram, performed by an expert cardiologist using standard techniques for evaluating the dimensions of the right ventricle and tricuspid gradients after a 20-minute rest. The tricuspid systolic pressure gradient was calculated using Bernoulli's modified equation[17]. Pulmonary artery pressure was calculated as the sum of the tricuspid gradient and the estimated right atrial pressure. PAH was defined as mean pulmonary artery systolic pressure > 25 mm Hg at rest or a tricuspid regurgitation velocity > 3 m/s or 2.5 m/s with unexplained dyspnea[18].

The institutional review board at the National University of Colombia (Universidad Nacional de Colombia) and Corporation for Biological Research (Corporación para Investigaciones Biológicas) approved the study design.

Clinical variables. Organ system involvement was defined using the criteria published by Medsger, *et al*[19] with slight modifications as follows: (1) renal involvement was defined as a rapidly progressive renal failure or serum creatinine level > 1.5 mg/dl and creatinine clearance < 45 ml/min determined on 2 occasions; or "renal crisis," defined as an acute rise (within 1 week) in diastolic blood pressure > 110 mm Hg associated with hematuria, proteinuria, papilledema, or microangiopathic hemolytic anemia, which required emergency measures, or which was fatal[20,21]; (2) articular involvement was defined as either swelling of ≥ 1 joint, tenosynovitis, presence of polyarthralgia, or palpable tendon friction rubs[22]; (3) skeletal muscle involvement was defined as detectable isolated muscle weakness or weakness associated with elevated serum creatine kinase with or without electromyographic or histologic changes of inflammatory myopathy[23]; (4) gastrointestinal involvement corresponded to the appearance and at least 3-month duration of 2 or more of the following characteristics: dysphagia, odynophagia or distal esophageal hypomotility or aperistalsis (documented by either cineradiographic or manometric study), typical small-bowel radiographic abnormalities, or colonic "sacculations," malabsorption syndrome, or repeated episodes of intestinal pseudoobstruction[21]; (5) pulmonary involvement was shown by the presence of any one of the following: bibasilar pulmonary fibrosis [bilateral reticular linear or reticulonodular densities, most pronounced in the lung bases, on standard chest radiograph with no other primary lung disease, or the presence of heterogeneous opacities such as reticular opacities, ground-glass opacities, or honeycombing in high resolution computed tomography (HRCT)][24], active pleuritis with pleural pain, and either a pleural friction rub or pleural effusion[21], diffusing capacity for carbon monoxide (DLCO) < 70% of predicted normal[25], forced vital capacity (FVC) < 70% of predicted normal[26], or PAH documented by echocardiogram, defined as peak systolic pulmonary artery pressure > 25 mm Hg at rest[18,27]; (6) cardiac involvement was defined as ventricular arrhythmia, heart failure, or persistent (> 2 months) moderate to large pericardial effusion detected by echocardiography[21,28]; (7) cutaneous involvement was associated with distal (limited SSc) or proximal (diffuse SSc) skin thickening, or calcinosis seen either radiographically or upon physical examination[29], sclerodactyly, puffy hands (sausage-like finger edema lasting > 6 months, or lasting a shorter time but followed by sclerodactyly)[30]

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or hypo- or hyperpigmentation, or microstomia, defined as a restriction in the range of motion of the mandible that resulted in a reduction in the normal maximal mouth opening measured as the distance between the incisal edge of the upper and lower first incisors that had a normal value ≥ 30 mm[31,32]; (8) peripheral vascular involvement was indicated by the presence of Raynaud's phenomenon (RP, characterized by episodic vasospasm with color changes — 2 of the 3 phases: pallor, cyanosis, erythema; pain and tautness/fullness in the digits following exposure to cold[33]) and/or digital pitting scars or loss of substance from the finger pad (depressed areas at the tips of the fingers or loss of digital pad tissue due to ischemia) and/or ulcerations and/or gangrene and/or telangiectasias[30,34]; (9) hematological involvement was indicated by either of the following: anemia (hemoglobin < 11.5 g/dl) or erythrocyte sedimentation rate (ESR) ≥ 28 mm/h[35,36]; (10) a positive antinuclear antibody test, including ACA, in which staining and distribution were determined by indirect immunofluorescence in HEp-2 cells and were considered positive at a titer > 1:80 dilution. Anti-topoisomerase I antibodies, anti-Ro, anti-La, and anti-Sm were measured by ELISA using commercial kits (Inova, San Francisco, CA, USA)[37].

Literature review. Electronic databases (Medline, PubMed, Scielo, LILACS and BIREME) were searched for all studies evaluating SSc in humans up to March 2007. The search strategy contained both MeSH terms and text words "systemic sclerosis" and "pulmonary hypertension." No other limits were employed. Studies were included if they met the following requirements: diagnosis of SSc was established using the classification criteria for SSc[1,16], the report was published in a peer-reviewed journal as a full paper, not as an abstract or summary, and provided enough information to be considered useful for comparison.

Statistical analysis. Data collection forms were compiled at the Corporación para Investigaciones Biológicas and systematically checked to assure their usefulness. Data were managed and stored using the SPSS program (V 13 for Windows; SPSS, Chicago, IL, USA). Results are presented as means ± standard deviation (SD) or percentages. Comparisons between means were performed by the Student t-test, and those between percentages were by chi-square test. A multiple logistic regression model was used to assess association between PAH and clinical and laboratory variables, adjusting for duration of disease and sex. Adjusted odds ratios (AOR) were calculated with 95% confidence intervals (CI). A p value < 0.05 was considered significant.

RESULTS

General clinical characteristics. A total of 365 patients were evaluated, 349 of whom were included for subsequent detailed analysis. Morphea, an incomplete data form, and inaccurate diagnosis were the basis for exclusion from the study. In 16 patients from the 5 rheumatology units there were incomplete clinical and echocardiogram data that excluded them from analysis. The main clinical and immunological variables for the 349 patients are depicted in Table 1.

The mean age at time of diagnosis was 54.5 ± 12.9 years. Patients were diagnosed as having SSc a mean of 6.2 ± 5.9 years after disease onset. Limited SSc was the most frequent cutaneous subset. All patients were Mestizo with Spanish ancestry, and the female/male ratio of incidence was 11:1. We found a high prevalence of telangiectasias, calcinosis, arthritis, esophageal involvement, RP, and positive staining for ACA (67%, 26%, 61%, 23%, 92%, and 93%, respectively). Significant differences based on city of origin were not observed. Ethnic and racial differences have been demonstrated to have an influence on the occurrence of the disease[3], and differences in ethnicity may account for diverse subtypes and organ involvement as reported by McNearney, *et al*[9]. Ethnic differences in HLA associations have also been reported in relation to specific autoantibodies[38-40].

Table 1. General characteristics of Colombian patients with SSc.

Feature	N = 349
Demographic	
Age at onset, yrs	54.5 ± 12.9
Female/male ratio	11:1
Female, %	92
Disease duration, yrs	6.2 ± 5.9
SSc subtype, %	
Diffuse	23.5
Limited	76.5
Organ system involvement, %	
Telangiectasias	67.6
Calcinosis	26.4
Raynaud phenomenon	92
Arthralgias or arthritis	61.3
Esophageal	23.2
Pulmonary	22.9
Cardiac	7.3
Kidney	5.7
Antibodies, %	
Antinuclear	97
Anticentromere	93
Anti-topoisomerase I	25

Pulmonary involvement. The total percentage of patients with pulmonary involvement was 22.9%. The percentages of patients with pulmonary fibrosis and PAH were 12.9% and 17%, respectively (6.8% with both conditions present). In a logistic regression model, after adjusting for disease duration and sex, 7 variables were independently predictive for PAH: pulmonary fibrosis, microstomia, gastroesophageal reflux, dysphagia, hypopigmentation, hyperpigmentation, and anemia (Table 2). Pulmonary functions tests (FVC or DLCO) were obtained in 49 patients, of whom 50% had an abnormal result. The low number of data precluded an accurate analysis.

Previous studies have reported several risk factors for PAH in patients with SSc (Table 3). Male sex was found to be a poor prognostic factor of pulmonary function loss in some studies[41-43], while Scorza, *et al*[44] identified that postmenopausal women were at an increased risk of PAH. Schachna, *et al*[45] and MacGregor, *et al*[18] found that older age at onset of SSc was a risk factor for PAH. African Americans had significantly lower pulmonary function test findings, more pulmonary involvement, and a higher frequency of diffuse cutaneous disease[9,46].

Greidinger, *et al*[47] found that African American ethnicity is a risk factor for SSc lung disease, and this result confirms early findings by Steen, *et al*[48] and Peters-Golden *et al*[49] that identified more severe lung disease as being associated with African American patients with SSc. Other investigators found that the measurements of DLCO and FVC during the initial evaluation were predictive of severe lung disease[48,50,51]; however, this observation is not unanimous[49,52-54]. This can be explained by methodological differences between studies and heterogeneity

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Table 2. Variables associated with pulmonary arterial hypertension (PAH) in Colombian patients with SSc.

Characteristic	PAH, N = 61 (%)	No PAH, N = 288 (%)	AOR (95% CI)	p
Age, yrs	56.2 ± 11.4	54.1 ± 13.2		NS
Duration of SSc, yrs	9.08 ± 6.6	5.6 ± 5.5		NS
Sex, female	54 (88.5)	266 (92.4)		NS
Anemia	10 (16.4)	8 (2.8)	5.4 (1.98–14.93)	0.001
Subsets of SSc				
Diffuse	16 (26.2)	66 (22.9)		NS
Limited	45 (73.8)	222 (77.1)		
Microstomia	22 (36.1)	36 (12.5)	3.3 (1.70–6.28)	< 0.0001
Hypopigmentation	20 (32.8)	41 (14.2)	2.4 (1.26–4.64)	0.008
Hyperpigmentation	17 (27.9)	48 (16.7)	2.15 (1.11–4.16)	0.02
Pulmonary fibrosis	24 (39.3)	21 (7.3)	7.37 (3.67–14.81)	< 0.0001
Gastroesophageal reflux	23 (37.7)	58 (20.1)	2.41 (1.31–4.43)	0.005
Dysphagia	36 (59)	92 (31.9)	2.7 (1.49–4.77)	0.001

AOR: adjusted odds ratio, NS: not significant.

Table 3. Factors for PAH in patients with SSc (literature review).

Series	Factor	OR (95% CI)	N
Scorza[44]	Postmenopausal condition	5.15 (2.26–11.72)	189
	Limited SSc	2.83 (1.51–5.28)	
Schachna[45]	Every 10 years of age at disease onset	1.52 (1.31–1.76)	274
	Late-onset, age ≥ 60 yrs	2.3 (1.32–3.99)	
MacGregor[18]	Male	2.4 (0.62–9.21)	930
	Limited SSc	18.1 (2.29–143)	
Steen[8]	New ulcers at time of PAH	5.23 (2.50–10.94)	212
	Past use of calcium channel blockers	0.37 (0.21–0.64)	
Morgan[51]	Low % predicted DLCO < 60	18.2 (3.5–93.8)	561
	Decreased FVC < 80%	4.1 (1.1–15.2)	
Plastiras[56]	Pulmonary fibrosis	6.78 (1.54–29.9)	114
	FVC < 80% of predicted	3.03 (1.1–8.35)	
	Duration of Raynaud's phenomenon	5.75 (1.9–17.41)	
McNearney[9]	African American ethnicity	4.34 (1.48–12.72)	203
	Disease duration	1.04 (1.02–1.07)	
	Anticentromere antibodies	0.08 (0.01–0.65)	
Yamane[61]	Elevated ESR	13.24 (0.73–421.3)	125
	Elevated IgG	6.4 (1.11–37.06)	
Jacobsen[58]	Right ventricular heart failure	12.4 (2.5–60)	174
	Diffuse SSc	7.8 (1.8–35)	
	% predicted DLCO < 40	4.8 (1.1–20)	
Mukerjee[11]	Hemodynamic indices of right ventricular heart failure	21	794
Chang[81]	Older age, limited skin disease, elevated pulmonary artery pressures at the time of initial evaluation, % predicted DLCO < 50	8.6*	361

* Calculated through longitudinal regression models. PASP: pulmonary artery systolic pressure, DLCO: diffusing capacity for carbon monoxide, FVC: forced vital capacity, ESR: erythrocyte sedimentation rate.

in patient populations[55]. Plastiras, *et al*[55] found that baseline FVC values measured within the first 3 years after disease onset may predict the subsequent rate of change in pulmonary function. In another study, these authors[56] observed that the presence of pulmonary fibrosis (demonstrated by HRCT, reduced FVC) and duration of RP (at least 3 years before development of SSc skin manifestations) were associated with PAH in patients with limited and diffuse SSc. Peters-Golden, *et al*[49] and Steen, *et al*[50] recognized that severe reduction in DLCO (< 55% of predicted) or increased FVC/DLCO ratio (> 1.4) are good predictors of PAH. Villalba, *et al*[57] found that desaturation during a 6-minute walk test provides additional information regarding severity of disease in SSc patients with pulmonary manifestations.

The presence of anti-topoisomerase I antibodies and severity of RP have been considered predictors of pulmonary func-

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tion loss[42,47,49,58]. However, some efforts to confirm the association of anti-topoisomerase I antibodies with function loss have not been successful[59]. Morelli, *et al*[60] and Steen, *et al*[48] found that the extent and severity of cutaneous disease were significantly associated with severe lung disease. Morgan, *et al*[59] found that positive urine protein was significantly predictive of an increased risk of developing severe lung disease. Yamane, *et al*[61] reported that an elevated ESR and increased immunoglobulin G were common features of SSc patients with PAH. Steen, *et al*[62] showed that patients who develop PAH have more severe peripheral vascular disease based on the increased severity of RP and of digital tip ulcers.

DISCUSSION

We analyzed the clinical and laboratory features of 349 patients with SSc. Notably, the percentage of patients with PAH in our study was 17%, which is higher than previously reported[13,61,63]. Several risk factors for PAH, including hypopigmentation and hyperpigmentation (AOR 2.4 and 2.15, respectively) were identified. Hyperpigmentation could be related to an increase in the keratinocyte production of endothelin-1 (ET-1), a 21 amino acid peptide with potent vasoconstrictive and proliferative effects. There is evidence indicating that ET-1 has certain trophic effects on human skin[64], and it is involved in both the multiplication of melanocytes and melanin synthesis in human melanocytes[65]. Rubens, *et al*[66] demonstrated that plasma concentrations of ET-1 and its precursor molecule correlate with the severity of PAH. Elevated levels of ET-1 are correlated with abnormalities of skin color, especially in severe cases and those with PAH. Hypopigmentation might represent the sequelae of inflammatory hyperpigmentation, although the underlying mechanisms and the variability among individuals for developing hypopigmentation are not well understood.

Our results confirm that pulmonary fibrosis is a risk factor for PAH[18,63,67,68] as well as gastroesophageal reflux and dysphagia. Both have been related to decreased FVC and DLCO values, presumably due to the microaspiration of gastric content into the lungs, which induces pulmonary parenchyma lesions, and by vagal stimulation from esophageal acid, causing bronchoconstriction[69]. Previous studies demonstrated that treatment of gastroesophageal reflux improves symptoms and pulmonary function test results for these patients, and this is consistent with results of other studies[70-75].

The other novel finding was the presence of microstomia (AOR 3.3) as a risk factor, which has not been previously reported as a risk factor for PAH. Anemia (AOR 5.4) was the unique laboratory risk factor for PAH in our series. Although no clear explanation exists for this finding, it could be attributed to hemolysis-associated PAH. It is likely that nitric oxide produced by endothelium would be immediately scavenged by hemoglobin and would therefore be incapable of paracrine diffusion from endothelium to vascular smooth muscle. Hemolysis is associated with the activation of downstream adhesion, prothrombotic and prooxidant pathways that may further participate in the endothelial dysfunction and vasculopathy of PAH. Other mechanisms may also contribute to the development of PAH-associated hemolysis, including chronic thromboembolism and induction of hypoxia-inducible factors such as vascular endothelial growth factor, ET-1, and erythropoietin[76-78]. Further studies are needed to confirm this association and to explore the hypothesis noted above explaining the link between anemia and PAH.

In patients with limited SSc, increased severity of RP predicts subsequent development of PAH[78], and Stupi, *et al*[79] reported a longer duration of RP in patients with PAH. Recently, Walker, *et al*[80] reported that onset of RP later in life was associated with a higher prevalence of more severe pulmonary fibrosis and PAH. Chang, *et al* found limited skin disease was a risk factor for PAH, but not RP[81].

Differences between diverse published series might be due to differences in diagnostic methods or methodological approaches, or to observation (interviewer) and ascertainment bias. However, genetic and environmental factors should also be considered. A genetic predisposition to SSc is suggested by reports of familial SSc, by animal models, and by disease-association studies, in which a wide variety of genes including those involved in fibrosis, in vascular function and structure, and in autoimmunity have been examined[82,83]. It is well known, however, that the association of genetic variants with complex diseases may vary according to ethnicity and admixture[85]. The term "complex genetic trait" defines those phenotypes not fitting patterns of Mendelian segregation, but showing a preferential familial clustering that cannot be exclusively explained by cultural or environmental effects. Possible causes underlying this departure from Mendelian laws are the presence of genetic heterogeneity, unknown or unmeasurable contributions of low-penetrance common alleles, and environmental factors[86]. Among the latter, solvents have been associated with SSc by several rigorous case-control studies that suggest a causal role, as reviewed[87]. Current data about other toxic agents (epoxy resins, vibrations, welding fumes) do not justify conclusions about their role in SSc[87].

In summary, while diversity in the frequency of specific manifestations of SSc is reflected in different regions of the world, PAH might be a frequent complication of SSc in Colombians regardless of subtype of disease. The clinical and laboratory risk factors identified would assist earlier diagnosis and guide decisions on therapeutic interventions on this critical complication of SSc. The reasons underlying the reported divergences in clinical and laboratory characteristics among patients from different ethnicities are not fully understood, but it is most likely that both genetic and nongenetic factors are responsible for them.

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