Ethnic Disparities Among Patients with Pulmonary Hypertension Associated with Systemic Sclerosis

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ABSTRACT. ***Objective.*** To examine a cohort of patients with systemic sclerosis (SSc) and pulmonary hypertension (PH) for ethnic disparities in clinical presentation, disease detection, or management.

Methods. Encounters of patients with SSc seen at the Medical University of South Carolina were recorded in a computerized database from November 1997 through January 2004. Patients were evaluated for discrepancy in disease manifestation and treatment. Evaluation criteria included patient ethnicity (by self report), age, disease duration from onset of first non-Raynaud's symptom, presence or absence of PH, incidence of diastolic dysfunction and left ventricular hypertrophy among patients with PH, severity of interstitial lung disease, and treatment course.

Results. African Americans were more likely than Caucasians to have diffuse cutaneous SSc (dcSSc) (69.9% vs 42.9%, $p < 0.001$) and they presented with PH (defined as right ventricular systolic pressure > 40 mm Hg by echocardiogram or mean pulmonary artery pressure > 25 mm Hg by right heart catheterization (RHC) at a younger age (60.9 yrs vs 49.0 yrs, $p < 0.001$). There were no ethnic disparities in time from onset of the first non-Raynaud's symptom to detection of PH, method of PH detection, or treatment modalities. Patients with PH were more likely to have diastolic dysfunction than those without PH (52.3% vs 35.9%, $p = 0.011$).

Conclusion. In this cohort of patients, African Americans were more likely to have dcSSc. Among patients with PH, African Americans presented at a younger age than their Caucasian counterparts. Incidence of diastolic dysfunction was higher in the PH population. There were no significant ethnic disparities in time of progression to PH or in treatment modalities employed in our cohort. (First Release May 15 2007; J Rheumatol 2007;34:1277–82)

Key Indexing Terms:
SYSTEMIC SCLEROSIS
ETHNIC GROUPS
PULMONARY HYPERTENSION
AFRICAN AMERICAN

Ethnic disparities in the incidence, prevalence, and clinical manifestations of systemic sclerosis (SSc, scleroderma) have been the focus of several epidemiologic studies[1-3]. Review of international population incidence and prevalence rates demonstrates that SSc occurs more commonly in the United States than in Britain, Iceland, or Japan[4]. Within the American population of patients with SSc, ethnic disparities have long been noted in the clinical presentation, severity, and progression of disease[1-3,5]. This includes differences in age at presentation, severity of organ involvement, autoantibody production, and prognosis. African American patients with limited or diffuse cutaneous SSc have a graver prognosis than their age and socioeconomically matched Caucasian counterparts[2,3,5].

In the United States the ethnic disparity in the incidence and prevalence of SSc has remained relatively stable over the last several decades, despite advances in diagnosis and therapy[4]. The incidence of diffuse cutaneous Ssc (dcSSc) among African Americans is approximately 20 cases/million/year, with a peak age of onset between 35 and 44 years. In contrast, the incidence of dcSSc among Caucasians is much lower, approximately 8 cases/million/year[4]. Peak age at onset is later in Caucasians, occurring between 45 and 54 years of age. Onset of limited cutaneous SSc (lcSSc) also occurs earlier in African American patients, with peak onset between 45 and 54 years of age in African American patients, as compared to peak onset between 55 and 64 years of age in Caucasians[4]. Diffuse disease occurs in about 70% of African American women with SSc, but only 30% of their Caucasian counterparts[4]. These patterns of presentation are similar in men. The attempt to uncover reasons behind this continued disparity in outcomes is central to epidemiologic studies of patients with SSc.

SSc-associated pulmonary hypertension (PH) is a nonin-

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Supported in part by a grant (1 P60 AR049459), entitled "Multidisciplinary Clinical Research Center for Rheumatic Diseases in African Americans" from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

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Accepted for publication February 13, 2007.

flammatory vasculopathy related to intimal proliferation of medium sized arteries, similar to the pathophysiology of primary PH[6]. Histological evidence of SSc-associated PH has been demonstrated in up to 50% of patients with SSc by postmortem examination[7]. It can occur as a primary process, more commonly in patients with lcSSc, or secondary to chronic hypoxia in the severe pulmonary fibrosis more often seen in patients with dcSSc[7-10]. PH contributes significantly to morbidity and mortality in the SSc population. As a result, patients are screened for the presence of PH with methods including pulmonary function test (PFT) and 6 minute walk testing, echocardiogram (ECHO), and right heart catheterization (RHC). Examination findings consistent with PH include a loud P2 heart sound and, in severe cases, evidence of right heart failure including lower extremity edema, hepatic congestion, and jugular venous distention.

A primary focus of our study was to evaluate our cohort of patients for the presence of PH, and discover any ethnic disparity in examination findings, progression of disease, or treatment at our institution. African American race is an independent risk factor for SSc lung disease, and several studies have shown a significantly increased incidence of PH in African American patients as compared with Caucasians[1,11-13]. Further, because deaths from scleroderma renal crisis have declined with the use of angiotensin converting enzyme inhibitors, pulmonary complications among patients with SSc are now the most common cause of mortality[1]. Our focus on PH is a reflection of its emerging importance as a cause of morbidity and mortality in SSc patients, especially the African-American population.

MATERIALS AND METHODS

Patients with SSc at the Medical University of South Carolina who consented to participate in a connective tissue disease computerized database (n = 328) were prospectively evaluated and medical data were entered into the database, which has been in existence since November 1997. Patients in our study were followed from the time of entry into the database until January 2004. All patients fulfilled the American College of Rheumatology preliminary classification data for systemic sclerosis, with diffuse and limited disease defined in accordance with the criteria outlined by LeRoy, *et al*[14].

Patients had an initial examination by physicians to categorize them into one of 4 potential types of disease. Those with cutaneous involvement proximal to elbows and knees were classified as dcSSc, whereas those with cutaneous involvement limited to skin distal to elbows and knees and face were classified as lcSSc[14]. Patients with lcSSc at high risk for developing dcSSc (those with positive Scl-70 antibody, presence of tendon friction rubs, and/or abnormal nailfold capillaroscopy) were classified as having uncertain disease. Patients with visceral organ characteristics of SSc but no skin thickening were classified as SSc sine scleroderma. Uncertain disease and SSc sine scleroderma were grouped with limited disease patients for statistical purposes. Historical data available at the time of entry into the database were included. Baseline PFT, 6 minute walk test, and ECHO were performed on patients with signs or symptoms suggesting PH or interstitial lung disease, including dyspnea on exertion, loud P2, basilar crackles on pulmonary auscultation, or lower extremity edema. Doppler ECHO and RHC reports available to investigators at the time of new patient evaluation and entry into the database were included; some may have had studies from outside institutions. All other studies were performed within our institution. In some patients multiple studies were performed at physician discretion to document the presence or degree of PH, and to guide therapy.

Factors analyzed in our study included patient ethnicity (by self report), age, disease duration from onset of the first non-Raynaud's symptom, presence or absence of PH, incidence of diastolic dysfunction among patients with PH, severity of ILD, and treatment course. Examination findings commonly associated with SSc were analyzed for ethnic disparity in occurrence. PH was defined as a peak right ventricular systolic pressure (RVSP) > 40 mm Hg by ECHO, or a mean pulmonary artery pressure (PAP) > 25 mm Hg by RHC.

Pulsed Doppler assessment of left ventricular mitral valve inflow was performed in the apical 4-chamber view by ECHO. The sample volume was measured from the tips of the valve leaflets. Peak velocities of E and A waves (m/s) and their ratio were obtained with left ventricular diastolic function defined as an inverted E/A ratio, which represents early and late filling of the left ventricle during atrial contraction. Pulsed Doppler assessment of the right ventricular tricuspid valve inflow was performed in the apical 4-chamber view by ECHO. The sample volume was measured at the tips of the leaflets of the tricuspid valve. Peak velocities of E and A waves (m/s) and their ratio were obtained with right ventricular diastolic function defined as an inverted E/A ratio, which represents early and late filling of the right ventricle during atrial contraction.

Pulmonary artery systolic pressure was calculated in all patients with Doppler recordings of tricuspid regurgitation using the modified Bernoulli equation (i.e., the pulmonary artery systolic pressure was considered as equal to 4 times the square of the peak velocity of the tricuspid jet with addition of the right atrial pressure (10 mm Hg). This equation has been shown to be comparable to values obtained at the time of heart catheterization[15].

Patients with suspected PH were evaluated by PFT with measures including forced vital capacity (FVC), diffusion capacity (DLCO), and FVC/DLCO ratio. Two different methods for calculating PH prevalence were used: the first assumed that patients without suspected PH (i.e., those with no signs or symptoms) did not have PH, while the second assumed that for patients without suspected PH, their PH status was truly unknown. In the first method described, patients without suspected PH were included in the denominators of the prevalence estimates, while in the second method, patients without suspected PH were not included in the denominators.

Statistical comparisons in disease classification (diffuse, limited, etc.) between Caucasian and African American patients with SSc were made using a chi-square test. All subsequent comparisons between Caucasian and African American patients adjusted for disease classification using Cochran-Mantel-Haenszel chi-square tests (for comparisons of categorical variables), or analysis of covariance models (for comparisons of continuous variables), as appropriate.

RESULTS

There were 788 encounters from 328 patients enrolled in the database, including 245 Caucasian and 83 African American patients (Table 1). There were highly significant ($p < 0.0001$) differences in the subtypes of SSc between ethnic groups; of the 245 Caucasian patients, 105 (42.9%) had dcSSc and 140 (57.1%) had lcSSc. There were 14 (5.7%) Caucasian patients with SSc sine scleroderma and 21 (8.6%) Caucasian patients were classified as having uncertain disease. There were 197 Caucasian female patients (80.0%) and 49 Caucasian male patients (20.0%). Of the 83 African American patients, 58 (69.9%) had dcSSc and 25 (30.1%) had lcSSc. There were 3 (3.6%) African American patients with SSc sine scleroderma and 10 (12.1%) with uncertain disease. There were 64 African American female patients (77.1%) and 19 African American male patients (22.9%) (Table 1).

There were no differences found in the methods used for

Table 1. Selected characteristics of 328 patients with SSc in the connective tissue disease database and mode of diagnosis of pulmonary hypertension.

	Caucasian, n = 245 (%)	African American, n = 83 (%)
Disease subtype*		
dcSSc	105 (42.9)	58 (69.9)
lcSSc	105 (42.9)	12 (14.5)
SSc sine scleroderma	14 (5.7)	3 (3.6)
Uncertain disease	21 (8.6)	10 (12.1)
Sex		
Female	197 (80.0)	64 (77.1)
Male	49 (20.0)	19 (22.9)
Mode of diagnosis of PH		
Echocardiogram	177 (72.2)	59 (71.1)
RHC	18 (7.4)	5 (6.0)
Presence of PH	44 (18.0)	19 (22.9)

* $p < 0.0001$. dcSSc: diffuse cutaneous SSc (cutaneous involvement proximal to elbows and knees); lcSSc: limited cutaneous SSc (cutaneous involvement distal to elbows and knees); SSc sine scleroderma: involvement of internal organs without skin involvement; Uncertain disease: lcSSc with + scl-70, tendon friction rubs and/or abnormal nailfold capillaroscopy (classified separately as they have high potential to develop diffuse disease).

detection of PH (Table 1). An ECHO was performed on 177 (72.2%) of the Caucasian patients with SSc and 59 (71.1%) of the African American patients with SSc. A RHC was performed in 18 (7.4%) of the Caucasian patients and in 5 (6.0%) of the African American patients. Those patients (n = 69) who did not have an ECHO or RHC were excluded from the analysis for PH and diastolic dysfunction. PH as defined by either ECHO or RHC was present in 44 (18.0%) of the Caucasian patients and in 19 (22.9%) of the African American patients, a difference that was not statistically significant, even with adjustment for the increased incidence of diffuse disease in African Americans.

Ethnic disparity was noted in the manifestations and age at detection of PH (Table 2). African American patients presented with PH at a younger age (49.0 yrs vs 60.9 yrs for Caucasians, $p < 0.001$) and had a trend toward a shorter disease duration from onset of non-Raynaud's phenomenon symptoms until diagnosis of PH (5.7 yrs vs 9.8 yrs in Caucasian, $p = 0.175$). On examination, there was no significant ($p > 0.05$) difference in the presence of an increased P2 (29.6% of the Caucasian patients with PH vs 26.3% of the African American patients with PH). A disparity was noted in the presence of lower extremity edema (61.4% Caucasian patients with PH vs 10.5% African American patients with PH, $p < 0.001$); however, there was no significant difference in the number of patients having ECHO evidence of right ventricular dilatation (29.0% of Caucasians vs 33.3% of African Americans).

There were no significant differences in the PFT results in Caucasian and African American patients with PH, in terms of FVC (mean 72.4% predicted in Caucasians vs 72.1% predicted in AfricanAmericans), DLCO (57.9% predicted in Caucasians vs 46.6% predicted in African Americans), or FVC/DLCO ratio > 1.6 (35.5% Caucasians vs 46.2% African Americans). There was no significant difference in the percentage of patients with PH having an FVC < 70% (an estimation of the presence of underlying restrictive lung disease) (42.9% of Caucasians vs 33.3% of African Americans).

Table 2. Physical findings by ethnicity among SSc patients with pulmonary hypertension.

	Caucasian, n = 44	African American, n = 19
Disease subtype (%)		
dcSSc	43.2	63.2
lcSSc	42.7	14.7
SSc sine scleroderma	4.9	5.9
Uncertain	6.1	8.8
Age at detection of PH, mean yrs (SD)*	60.9 (12.7)	49.0 (11.5)
Yrs between diagnosis of SSc and detection of PH, mean yrs (SD)	9.8 (9.1)	5.7 (6.0)
Mean PA pressure, mean mm Hg (SD)	48.5 (13.7)	51.1 (12.2)
Increased P2 (%)	29.6	26.3
Exertional dyspnea (%)	97.7	100
PFT results (%)		
Mean FVC	72.4	72.1
FVC < 70%	42.9	33.3
Mean DLCO	57.9	46.6
DLCO < 80%	79.3	92.3
DLCO < 60%	62.1	84.6
DLCO < 40%	24.1	38.5
FVC/DLCO > 1.6	35.5	46.2
Right ventricular dilation on ECHO (%)	29.0	33.3
Lower extremity edema (%)*	61.4	10.5

* $p < 0.001$. PA: pulmonary artery; FVC: forced vital capacity; DLCO: diffusing capacity (carbon monoxide). ECHO: echocardiogram.

Although patients with PH were significantly more likely to have diastolic dysfunction than patients without PH (61.4% of patients with PH vs 39.5% of patients without PH, $p = 0.005$), there was no ethnic disparity with respect to diastolic dysfunction (61.1% of Caucasians with PH vs 61.5% of African Americans with PH). There was a significant increase in the incidence of left ventricle hypertrophy (LVH) in patients with PH (45.8% of patients with PH vs 28.8% of patients without PH, $p = 0.017$), with no significant difference in the presence of LVH between Caucasians (48.8%) and African Americans (39.9%) with PH.

There were no significant disparities between Caucasian and African American patients with respect to management or treatment of PH, including home oxygen (40.9% Caucasians vs 21.1% African Americans), warfarin (20.5% Caucasians vs 21.1% African Americans), intravenous prostacyclin (Flolan®) (11.6% Caucasians vs 15.8% African Americans), and bosentan (Tracleer®) (20.9% Caucasians vs 15.8% African Americans) (Table 3). No patients were treated with inhaled iloprost, trepostinil, or sitaxsentan. Some patients were treated with sildenafil, but because of small numbers, these patients were not included in analysis.

Table 3. Treatment of PH by ethnicity among SSc patients with pulmonary arterial hypertension.

	Caucasian n = 44	African American n = 19
Home oxygen (%)	40.9	21.1
Warfarin (coumadin) (%)	20.5	21.1
Iloprostanol (Flolan®) (%)	11.6	15.8
Bosentan (Tracleer®) (%)	20.9	15.8

DISCUSSION

There continues to be an ethnic disparity with regard to progression of disease among patients with SSc. The tendency toward diffuse disease in African American patients is partially responsible for this discrepancy, but other factors contribute as well. Independent risk factors for development of scleroderma lung disease including the presence of dcSSc and autoantibodies to topoisomerase 1 are more common among African Americans[1]. African American patients more often develop severe restrictive lung disease, defined as FVC < 50% predicted, and have higher rates of PH than Caucasians[3]. This pattern persists even within the subset of patients who are positive for anti-topoisomerase 1, an autoantibody associated with diffuse skin disease and pulmonary fibrosis[2]. Our study results support published data on age of onset and progression of disease in African Americans, but within our population there were no significant differences between ethnic groups with regard to severity of lung disease as measured by FVC and DLCO. We did not evaluate for the presence of autoantibodies to topoisomerase-1 in all of the patients in our cohort, and therefore did not include this variable in our statistical analysis.

Results of our study demonstrate that 22.9% to 31.7% of our African American cohort had PH, depending on the algorithm used to estimate prevalence. This percentage may be somewhat higher than those from previous studies in which African American patients with SSc had an incidence of PH ranging from 4% to 23%[3,12,16]. Mild PH is generally defined as RVSP 36 mm Hg-50 mm Hg by Doppler ECHO[17]. Past studies have used RVSP 30 mm Hg-35 mm Hg by ECHO as a screening cutoff for PH[18-20]. However, 2 recent studies have advocated a more conservative definition of PH in Doppler ECHO screening to avoid overestimation of prevalence[21,22]. A multicenter study of community-based rheumatology practices by Wigley, *et al* used RVSP > 40 mm Hg for screening of the PH population[21]. Mukerjee, *et al* evaluated 137 patients with SSc suspected to have PH by ECHO findings or isolated low DLCO by RHC. Comparison of Doppler ECHO values and PAP values by RHC revealed that at tricuspid gradient (TG) > 40 mm Hg, positive predictive value of having PH was 92%, with a sensitivity of 58% and a specificity of 87%[22]. However, even at a TG < 30 mm Hg by ECHO, a small percentage of patients were found to have PH by RHC. As the focus of our study is detecting early PH, we have elected to use RVSP > 40 mm Hg (which would include RA pressure correction of 10 mm Hg) to define PH in our analysis.

An important new finding in our study is the earlier onset of PH among African American patients, even when values were adjusted for diffuse disease. In addition, there was a trend toward faster rate of progression of disease in our African American patients, with the average time between onset of first non-Raynaud's symptom and diagnosis of PH being 5.8 years, compared to 9.8 years in Caucasian patients (p = 0.175). There are at least 2 studies demonstrating significantly higher rates of PH in African Americans, but there is very little discussion in the literature regarding ethnic disparities in the rate of PH within the population of patients with SSc[12,13]. Faster rate of PH progression may partially explain why African Americans with PH have poorer outcomes than their socio-economically matched Caucasian counterparts.

Our study found no ethnic disparity in most examination findings in patients with PH, with the exception of a significant increase in the likelihood of Caucasians having lower extremity edema. We could not attribute this finding to calcium channel blocker use, as these drugs are more commonly taken in our African American patient population. This finding is especially surprising given that there was no significant ethnic disparity in the presence of a loud P2 sound or in the incidence of right ventricular hypertrophy or dilatation on ECHO. Whether this examination disparity has an effect on outcomes is unclear.

Commonly used therapies for PH include oxygen, warfarin, intravenous prostacyclin (Flolan), and endothelin receptor antagonists such as bosentan (Tracleer)[23]. We found no ethnic disparity in our cohort with regard to number of patients treated with oxygen, warfarin, prostacyclin, or bosentan. Therapies including trepostinil sodium (Remodulin®), inhaled iloprost (Ventavis®), sildenafil citrate (Revatio®), and sitaxsentan sodium (Thelin®) were not evaluated as very few of our patients were treated with these agents. Therefore we cannot comment on ethnic disparities in treatment with or response to these modalities. The small number of patients in our database who were treated with these medications likely reflects the fact that many of our patients were diagnosed before the widespread availability of these agents.

There is limited information regarding the prevalence of diastolic dysfunction in patients with SSc. Further, we found no study evaluating diastolic dysfunction and ethnicity in patients with SSc and PH. One case series of 27 patients with SSc (ethnicity not reported) and dyspnea who were evaluated by RHC and LHC found that the majority had evidence of diastolic dysfunction, and only a minority had PH[24]. The authors conclude that diastolic dysfunction is a common and underrecognized cause of dyspnea in patients with SSc. A similar study of 34 Japanese patients with SSc evaluated by myocardial perfusion imaging found diastolic dysfunction was present in over half of cases and correlated with the severity of cutaneous disease[25].

We found a significant correlation in patients with SSc and PH with diastolic dysfunction and the presence of LVH by ECHO. However, no significant differences with regard to ethnicity were found. The significance of diastolic dysfunction in our patients with PH is not entirely clear. Some authors have argued that diastolic dysfunction does not exist independent of left ventricular pathology in patients with SSc[26]. Others argue that even in patients with similar ejection fractions to those of controls, diastolic dysfunction is more prevalent in patients with SSc, and that there is an association between increased pulmonary pressures and diastolic dysfunction[27]. Therefore, it is not surprising that we show an increased incidence of diastolic dysfunction in our PH cohort. It is interesting, however, that there is no predominance of diastolic dysfunction in our African American patients despite their earlier onset of disease and faster progression. This finding adds emphasis to the need for further study of the role of diastolic dysfunction in this population.

There are several limitations to our study. We are a tertiary and quaternary referral center for patients with SSc. Therefore, our population overall may be more seriously ill than most patients seen in community practices, which may lead to a higher prevalence of PH in our cohort. However, it is notable that our prevalence is similar to that of the UNCOVER study (a community-based prospective analysis of SSc-associated PH patients)[21]. Further, socioeconomically underprivileged patients make up a significant percentage of our population. These patients often have limited access to health care and medications, which may affect the progression of their disease. Another issue in our study is the limited number of patients in our cohort who underwent RHC, the accepted gold standard for diagnosis of PH. Even using a conservative definition of PH, we may have overestimated disease prevalence. Lack of RHC data including pulmonary capillary wedge pressure and cardiac output makes it difficult to definitively identify patients with left heart disease and elevated left sided pressures that contribute to PH. Complicating this is the potential variability in quality of ECHO readings because of multiple technicians and intraobserver differences in reading. In addition, approximately one-fifth of our PH patients were treated with oxygen after the diagnosis of PH was made. It is possible that these patients had worsening of their disease as a result of their hypoxia. ECHO or RHC data were not available on all our patients with SSc. The ECHO and RHC were obtained at attending physician discretion, and selection bias likely affected the detection of PH incidence in this cohort. Finally, not all patients were examined for the presence of PH as some patients were enrolled in the database at the time of their initial encounter but did not return for followup visits.

We found that the African American patients in our cohort are more likely to have diffuse disease and develop PH at a younger age than their Caucasian counterparts. There were no ethnic disparities in the detection of patients with PH or in treatment modalities used. Caucasians were more likely to have lower extremity edema than African Americans, but no more likely to have ECHO evidence of right heart strain. There was no ethnic disparity in prevalence of diastolic dysfunction measured by ECHO, but patients with PH were significantly more likely to have diastolic dysfunction and LVH. Further study of our cohort is needed to determine if the presence of diastolic dysfunction in patients with PH independently affects survival, and whether there are ethnic disparities in response to newer therapies for PH and in survival.

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