Prevalence and Predictors of Pulmonary Artery Hypertension in Systemic Sclerosis

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Abstract

Introduction: Development of pulmonary artery hypertension (PAH) worsens the prognosis of systemic sclerosis (SSc). There is paucity of data on PAH in patients with SSc in India. We have attempted to determine the prevalence and predictors of pulmonary artery hypertension in systemic sclerosis using noninvasive cardiopulmonary evaluation.

Objectives: (1) To study the prevalence of PAH in SSc (2) To study the predictors of PAH in SSc (gender, age of onset of disease, duration of disease, extent of skin involvement, digital infarcts/ulcer, interstitial lung disease.

Material and Methods: Clinical and functional characteristics of 100 patients of systemic sclerosis who had undergone screening echocardiography to detect pulmonary artery hypertension were studied.

Results: PAH was found in 32% patients on 2D-echocardiography. Prevalence of PAH did not differ between patients with limited cutaneous SSc (lcSSc) and patients with diffuse cutaneous SSc (dcSSc). On multiple logistic regression analysis, none of the studied variables was found to be independent predictor of PAH in SSc.

Conclusion: PAH in SSc occurs in significant proportion of patients without any “red flag signs” in early stages. Non-invasive screening of patients with SSc for PAH will help in early diagnosis and appropriate timely therapeutic intervention before significant end-organ damage occurs.

INTRODUCTION

SSc is a multisystem autoimmune disease characterized by fibrosis, vasculopathy and altered immune status. Over the period of time with the availability of angiotensin converting enzyme inhibitors frequency of scleroderma renal crisis associated deaths have significantly declined, while pulmonary complications (interstitial lung disease and pulmonary artery hypertension) still account for 25% of all cause of death in this group of patients. PAH in SSc can be an isolated precapillary pulmonary artery hypertension or secondary in association with interstitial lung disease (ILD). PAH developing in SSc is particularly severe and one year survival following diagnosis is 55%. Since outlook for patients with SSc related PAH is worse if left untreated speedy diagnosis is vital. Therefore, the British Cardiac Society guidelines recommend Trans thoracic echocardiography to screen SSc patients for PAH every year.

Various risk factors like increasing age, male gender, digital pits, infarcts and black race have been implicated in the development of pulmonary arterial hypertension in scleroderma.

This study was carried out with the following aims and objectives (1) To study the prevalence of PAH in SSc (2) To study the predictors of PAH in SSc (gender, age of onset of disease, duration of disease, extent of skin involvement, digital infarcts/ulcer, interstitial lung disease.

MATERIAL AND METHODS

It was a cross sectional study carried out in the department of medicine from year 2004-2007 at AIIMS, New Delhi. Patients were recruited from out patient department and wards of medicine and dermatology, and the rheumatology clinic.

Inclusion criteria: (1) All patient of scleroderma fulfilling ACR criteria (1980) (2) age of disease onset more than 13 years (onset of disease was marked by appearance of first symptom of SSc i.e. Raynaud’s
phenomenon, skin tightening).

Exclusion criteria: (1) overlap syndromes (2) patients who refused consent.

Project was cleared by departmental review committee. Written consent was obtained from all patients. All patients underwent clinical, serologic, and noninvasive cardiopulmonary evaluation including chest radiography, electrocardiogram (ECG), pulmonary function test (PFT) and 2D-echocardiography. HRCT was done wherever indicated. Functional status of patient with pulmonary arterial hypertension was assessed according to WHO classification of functional status of patients with pulmonary arterial hypertension.6

Echocardiographic evaluation

Non-imaging continuous wave Doppler signals with Doptek at 3.5/2.7 MHz transducer was used for doing echocardiography. Vasodilators prescribed for the treatment of Raynaud’s phenomenon were stopped six hour prior to the study. Special attention was given to detection of tricuspid regurgitation (TR). To estimate pulmonary artery systolic pressure (PASP), maximum transtricuspid pressure gradient was calculated using the simplified Bernoulli’s equation.10

\[ Dp = 4V^2 \]

where \( Dp \) is the trans tricuspid gradient and \( V \) is the peak velocity measured. The estimate of right atrial pressure, 10 mm Hg was added to the pressure gradient to calculate the right ventricular systolic pressure, which was considered equal to the PASP in absence of right ventricular outflow obstruction. The right ventricular Acceleration time (ACT) was also recorded. Mean pulmonary artery pressure was derived from right ventricular acceleration time (ACT) by formula

\[ Dp = 4V^2 \times ACT \text{ where } ACT \text{ is in milliseconds.} \]

Patient considered having pulmonary hypertension if they fulfilled either of the two criteria: transtricuspid gradient more than 35 mm Hg or right ventricular acceleration time of less than 90 millisecond.

Statistical analysis

Statistical analysis was done using SPSS 11.5 and Excel statistical software. Two - tailed P values less than 0.05 were considered statistically significant. Results were expressed as frequencies and percentages for binary and categorical variables and as mean ± standard deviation (SD) for continuous variables. Comparative analysis was performed using chi square test or Fisher exact tests for categorical variables and unpaired student’s t test for continuous variables. The parameters were subjected to multivariate logistic regression analysis to assess their potential association with PAH after adjusting for each other.

**RESULTS**

Demographic and clinical characteristic

Among the 100 patients, there were 87 females (87%) and 13 males (13%). The mean age of onset of disease was 29.4 ± 11.38 years (IQR 20.25, 37). The mean duration of disease from onset of first symptom to the time of echocardiography was 7.15 ± 5.48 years (IQR 3, 10.75). There were 39 (39%) patients of dcSSc and 61 (61%) patients of lcSSc in the study population. The mean duration of disease was 7.9 ± 5.5 years and 6.7 ± 5.45 years in dcSSc and lcSSc respectively (p>0.05). Clinical characteristics of 100-studied patient of SSc are given in Table 1. Most common clinical presentation at onset of disease was Raynaud’s phenomena followed by non healing digital ulcers. Pigmentary skin changes were present in 72% patients, which included salt pepper pigmentation, vitiligo and generalized hyperpigmentation. Pseudo obstruction and dysphagia was present in 5% and 43% patients respectively. Only 1 patient had features of malabsorption. None of the patients complaint of symptoms suggestive of carpal tunnel syndrome, trigeminal neuralgias, stroke, oliguria or hematuria. Five out of thirteen males had erectile dysfunction. 11% of patients had postural hypotension and found to have autonomic neuropathy on cardiovascular autonomic function tests.

In clinical examination, elevated JVP and loud P2 were found in 3% and 21% respectively. ECG showed features of RVH in only 13/32 (42.62%) patients who had PAH. Commonest feature was poor progression of R waves. Anti Nuclear antibodies were present in 92% of patients. Comparison between the two groups dcSSc and lcSSc is shown in Table 2.

There was statistically significant difference between the two groups in terms of dyspnea (NYHA III or IV) which was more commonly complaint off in dcSSc (p<0.05). Similarly, volar fat pad loss, acro-osteolysis and telangiectasia were more common in dcSSc (p<0.05).

**Echocardiography**

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Western Data (multiple studies)</th>
<th>AIIMS data N=100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of disease onset</td>
<td>38-53yrs</td>
<td>29.5yrs</td>
</tr>
<tr>
<td>% of females</td>
<td>83-87%</td>
<td>87%</td>
</tr>
<tr>
<td>Raynaud’s Phenomenon</td>
<td>92-100%</td>
<td>97%</td>
</tr>
<tr>
<td>Skin thickening</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Sclerodactyly</td>
<td>90%</td>
<td>99%</td>
</tr>
<tr>
<td>Digital pits/Ulcers</td>
<td>25-66%</td>
<td>78%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>18-68%</td>
<td>10%</td>
</tr>
<tr>
<td>GERD</td>
<td>80-90%</td>
<td>51%</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>45%</td>
<td>56%</td>
</tr>
<tr>
<td>PAH</td>
<td>25%</td>
<td>32%</td>
</tr>
<tr>
<td>SFC</td>
<td>0-1.2%</td>
<td>0%</td>
</tr>
<tr>
<td>ILD</td>
<td>80-90%</td>
<td>61%</td>
</tr>
<tr>
<td>SScc symptoms</td>
<td>20-30%</td>
<td>33%</td>
</tr>
<tr>
<td>Proximal muscle weakness</td>
<td>60-80%</td>
<td>21%</td>
</tr>
<tr>
<td>Tachyarrhythmia, conduction disturbances</td>
<td>50%</td>
<td>Not studied</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>67-82%</td>
<td>30%</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>11-42%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Tricuspid regurgitation was present in 45% (45/100) of patients but only 18% had transtricuspid regurgitant gradient more than 35mm Hg. Right ventricular acceleration time was less than 90 millisec in 30% (30/100) SSc patients. Only 16% patients fulfilled both criteria for diagnosis of pulmonary arterial hypertension. Various echocardiographic criteria for diagnosing PAH are shown in Figure 1. Estimated mean PAP for the study population based on Mahan’s equation was 25.1 + 11.05 mm Hg.

The prevalence of pulmonary arterial hypertension was found to be 32% (95% CI, 0.22–0.42), calculated using standard error of proportion in total population. In subgroups, the prevalence was 38.5% and 27.9% in diffuse cutaneous and limited cutaneous SSc respectively which was not statistically significant (p>0.05).

Mean pulmonary arterial pressure increased with increasing age of onset of disease when entire population was considered, although this was not statistically significant In subgroup analysis (dcSSc vs lcSSc), there was statistically significant increase in mean pulmonary arterial pressures with increasing age of onset in dcSSc (p=0.01) but there was no statistically significant increase in occurrence of PAH (p=0.627).

Although there was no statistically significant increase in prevalence of pulmonary arterial hypertension with increasing age of onset of disease when entire population was considered, by trend chi square test (p =0.105), but there was significant increase in PAH from 3rd decade onwards as shown in Figure 2. PFT results (FEV1, FVC and FEV1/FVC ratio) were available for all 100 patients but diffusing lung capacity and total lung capacity can done only in 76 patients because of technical reasons.

HRCT chest was done in 81 patients with suspected ILD, out of which only 64 patients had radiological evidence of ILD. Therefore, only 64% patients had ILD. ILD and PAH both were present in 29% (29/100) patients while 3% (3/100) had only PAH.

On using one-way analysis of variance (ANOVA), presence of ILD, telangiectasia, acro-osteolysis, and duration of disease >6years had significant effect on occurrence of PAH (p>0.05). Multiple Logistic regressions for parameters showing significant effect were used to nullify the effect of individual parameters on other (Table 3). None of them remained significant after adjusting for each other.

**DISCUSSION**

The prevalence of PAH in our study population was 32%. The prevalence fell to 18% when we used only echocardiographic tricuspid gradient cut off value of ≥35 mm Hg to define PAH. Prevalence of PAH varies from 5-35% in various studies depending upon the different methods and diagnostic criteria used for diagnosis. 

The mean from several studies is approximately 15%. 

Prevalence of PAH in our study is high probably because of inclusion of right ventricular acceleration...
time ≤ 90 millisec as one of the diagnostic criteria and our being tertiary care center could therefore have had more severe SSc. The cut off value of 35mm Hg for transtencuspid pressure gradient which we used had sensitivity of 75%, specificity of 66% and positive and negative predictive value of 85% and 50% respectively. We could not confirm our finding with right heart catherization because of ethical reasons.

It is well known that dyspnoea is one of the most important symptoms of PAH. But, majority of patients remain asymptomatic in the early stage of PAH. Our study population had early age of onset of disease (29.4 ± 11.38 years) as compared to western literature. This is important because previous studies have shown that later the age of onset more likely are the chances to develop pulmonary arterial hypertension. Onset of Raynaud’s phenomenon later in life was also associated with a higher prevalence of more severe disease manifestations such as pulmonary fibrosis and PAH. Similarly, mean age of onset were 28.6 ±10.5 and 29.9 ± 11.9 year in diffuse and limited cutaneous SSc (p> 0.05) as found in previous study but non Raynauds manifestation tends to occur early in Diffuse Cutaneous scleroderma.

In scleroderma, aging may promote the development of PAH via several important pathogenic pathways. First, aging tends to reduce endothelial release of nitric oxide and endothelium dependent relaxation by acetylcholine. Second, spontaneous endothelial injury, possibly as a result of the generation of excess oxygen-derived free radicals and defective in vivo endothelial repair mechanisms, increases in older individuals. Third, changes in immune reactivity with aging (termed immunescence) include aberrant T-cell proliferation and increased production of autoantibodies. These aging related changes in vascular biology may render the pulmonary arterial tree particularly susceptible to the pathophysiologic mechanisms observed in scleroderma.

Presence of Raynauds phenomena and digital pitting ulcers are almost comparable to other previous studies. Telangiectasies were not that common as western studies, probably of difficulty to pick them in dark complexion Indian population. Calcinosis was also not commonly observed in our study group when compared to western data.

Comparing the clinical features within the two groups, Dyspnea (NYHA III or IV) was more commonly complaint off in dcSSc, probably because of tightening of skin over chest wall and involvement of lung by interstitial lung disease. Similarly, volar fat pad loss, acro osteolysis and telangiectasia were more common in Diffuse cutaneous (p<0.05). Digital ulcers, ILD, esophageal hypomotility, musculoskeletal impairment, was more common in patients with dcSSc but the difference was not statistically significant.

In our study, it was found that there was no significant difference between the two groups with regards to pulmonary arterial hypertension which was similar to other studies.

An attempt to classify pulmonary arterial hypertension into Isolated and secondary PAH was made based on presence or absence of interstitial lung disease on HRCT chest. We found that the prevalence of secondary pulmonary arterial hypertension was more compared to isolated may be due to less duration of disease predominantly in limited cutaneous group. Previously studies have shown that the prevalence of isolated pulmonary arterial hypertension was more in limited cutaneous disease 15 years after onset of disease. Plastiras et al. showed that pulmonary fibrosis on thoracic computed tomography and duration of raynauds more than 3 years as independent risk factors for development of pulmonary arterial hypertension. None of our variable studied as predictors of PAH in SSc remained statistically significant after adjusting for confounders.

The strength of our study is large cohort of SSc, collection of extensive data on potential confounders and all patients underwent screening echocardiography. Nevertheless, limitation of our study also needs to be addressed. (1) There can be referral bias leading to manifestation of more severe disease resulting in high prevalence of PAH. (2) We could not confirm our findings of echocardiography with right heart catheterization because of ethical issues. (3) We could not classify PAH (isolated and secondary) as radiological grading of pulmonary changes on HRCT of chest is not complete. But, we are in the process of grading the extent and severity of lung involvement on HRCT of chest.

In conclusion, despite these limitations, this study highlights the need to routinely screen all the patients with SSc for PAH, so that they can be detected early and intervened prior to development of irreversible pulmonary vascular disease. Echocardiography as an adjunct to clinical evaluation is the optimal current screening approach to identify patients with PAH.

REFERENCES


