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Prevalence of pulmonary hypertension in chronic simple silicosis patients and its correlation with smoking history, occupation type, age and duration of silica exposure

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Abstract

Silicosis is a preventable occupational health hazard with the potential for permanent physical disability and increased socio-economic burden. Pulmonary hypertension (PH) secondary to chronic respiratory diseases signifies a poorer prognosis and transthoracic echocardiography (TTE) has proven its usefulness as a screening tool for PH diagnosis. The objectives were to determine PH prevalence in chronic simple silicosis patients through TTE screening and correlate PH prevalence with smoking status, occupation type, age, and duration of silica exposure (DSE). We enrolled 104 patients in the study based on occupational exposure to silica dust and radiologic confirmation of chronic simple silicosis. The study sample was divided into significant smokers (SS group) and insignificant smokers (InS group) based on ≥10 pack years smoking history, and into drillers and dressers based on occupation type. TTE examination was performed to measure resting mean pulmonary artery pressure (mPAP) and the patients were classified into: no PH (mPAP≤20 mm Hg), borderline PH (mPAP>20 and <25 mmHg), and PH (mPAP≥25). PH prevalence was 25% in study subjects (26/104); 29.6% (16/54) among SS group *vs.* 20% (10/50) among InS group (0.52); and 34.2% (14/41) among drillers *vs.* 19.1% (12/63) among dressers (p=0.024). Mean age and mean DSE among SS and InS groups were comparatively similar, while they had lower values among dressers against dressers with no statistical significance. Logistic regression analysis established a significant association of PH prevalence with higher age in the study sample, SS group, and drillers group, while a significant association of PH prevalence with longer DSE was only seen in the study sample. PH prevalence was significantly associated (p=0.007) with the SS-driller group when comparing TTE findings with combined smoking and occupation type-based groups. This study has shown PH prevalence in chronic simple silicosis patients at alarming levels, having associations with driller occupation, older age, and longer DSE with varying results among groups and complex interplay with smoking exposure, suggesting the need for large sample-based molecular and genetic studies. Including TTE in the initial work-up of silicosis patients will promote timely intervention and reduce morbidity and mortality with a high benefit-cost ratio.

Introduction

Silicosis is a fibrotic disease of the lungs attributable to occupational inhalation, retention, and pulmonary reaction to res-

pirable crystalline silica (RCS), usually as quartz and other crystalline forms (cristobalite and tridymite) [1,2]. Silica is found in the earth's crust and in construction materials. Its exposure is related to occupational activities such as glass manufacturing, mining, drilling, blasting, and chisel dressing. Silicosis has been classified into chronic simple, accelerated, and acute silicosis based on disease severity, radiographic pattern, onset, and rapidity of progression and often relates to duration of exposure [2-8]. Stone mine workers are generally classified into drillers, dressers, and laborers based on employed work [9,10].

Globally, an estimated 2.02 million people die each year from work-related diseases [11]. In India, about 11.5 million workers employed in various industries are exposed to RCS in both organized and unorganized sectors [12]. Studies have shown that silicosis prevalence rates are 54.6% among slate pencil workers, 35.2% among stonecutters, and 3.03% among coal worker's pneumoconiosis [13-15]. The western part of Rajasthan has a large number of workers engaged in sandstone mines, with a prevalence of silicosis in Jodhpur quarry workers of around 9.9% [16].

Inhaled silica particles induced inflammation as well as direct invasion of ultra-fine silica particles through the pulmonary epithelium into the vascular bed may directly affect the integrity of the vascular endothelium [17-19]. Pulmonary hypertension (PH) is a manifestation of chronic hypoxia secondary to chronic respiratory disorders [20]. PH is defined by mean pulmonary artery pressure (mPAP) ≥25 mmhg at rest measured by right heart catheterization (RHC) [21]. At the 6th World Symposium on Pulmonary Hypertension, it was proposed that the mPAP threshold used to define PH should be lowered from ≥25 mmHg to >20 mmHg [22]. Silicosis patients are usually assessed based on history, clinical evaluation, radiology, and spirometry, while cardiac assessment is mostly ignored, especially in patients with early stages of the disease, while the presence of PH in these patients worsens the prognosis [23].

The symptoms of PH are non-specific [24]. The electrocardiography is relatively specific (70-86%), but not sensitive (51-55%) to be used as a screening tool and does not correlate with the severity of PH [25-27]. Though RHC is considered the gold standard for diagnosis of PH, but since it is an invasive technique and has a high cost, it cannot be used as a screening tool. Transthoracic echocardiography (TTE) is a non-invasive, cheaper, and easily available investigation that qualifies as the best screening tool for the assessment of PH in suspected patients [28].

In this study, TTE screening of chronic simple silicosis patients was done to determine the prevalence of PH. Secondary objectives were to correlate PH prevalence with smoking history, occupation type, age, and duration of exposure.

Materials and Methods

Study center

The study was conducted over a period of 12 months in a tertiary care center for respiratory diseases in the western part of Rajasthan, India.

Study design

This was a cross-sectional analytical study, which was carried out to estimate the prevalence of PH in chronic simple silicosis patients through TTE. This study was approved by the Ethical Committee of Dr. Sampurnanand Medical College, Jodhpur (approval document no. F.1/Acad/MC/JU/16/7814 dated May 3, 2016).

Study sample

Patients above 18 years of age either admitted as inpatients or attending the outpatient clinic of the Department of Pulmonary Medicine, who had a history of occupational exposure to silica dust and presented with history, signs, and symptoms suggestive of silicosis (asymptomatic, dyspnea at rest or exertion or dry cough) were enrolled after having informed consent to participate in the study. 110 patients were screened on the basis of the history of silica exposure and postero-anterior chest radiographs compared with the International Labor Office classification of radiographs of pneumoconiosis by a team of two pulmonologists and one radiologist to find patients with nodular opacities of less than 10mm (ILO category P,Q,R) consistent with diagnosis of chronic simple silicosis. Six patients were excluded from screening because their radiographs did not fulfill the criteria for chronic simple silicosis. The remaining patients (n=104) were further evaluated with detailed history, especially regarding smoking, type of occupation, age, and duration of exposure. Therefore, the study sample was divided into two groups: significant smokers (SS) with a smoking history equal to or above 10 pack years and insignificant smokers (InS) with a smoking history below 10 pack years (SS and InS were used as nomenclature to groups, not as definitions) [29]. Patients with clinical features suggestive of infection, or malignancy (cough with expectoration, fever, sudden onset dyspnea and/or tachypnea, reduced appetite, significant weight loss, confusion, hemoptysis, *etc*.); chest radiograph suggesting fibrosis, pleural effusion, emphysema, bulla, pneumothorax, consolidation, collapse, rib cage fractures, kyphoscoliosis, or mass; patients with HIV infection, primary cardiac diseases and other systemic diseases (cerebrovascular diseases, connective tissue diseases, portal hypertension, drugs, toxins, pulmonary veno-occlusive disease, *etc*.) which may have pulmonary and cardiac manifestations and patients who have denied informed consent were excluded.

These patients were then referred to the cardiology department where TTE was performed using GE Vivid E9 echocardiography machine. TTE provides several variables which correlate with right heart hemodynamics including systolic pulmonary artery pressure (sPAP) which was based on the measurement of maximum tricuspid regurgitation velocity, peak pressure gradient of tricuspid regurgitation, and a fixed value of 10 mm Hg for right atrial pressure was assumed. Chemla's formula [mPAP = 0.61x (sPAP) + 2mm Hg] was used to calculate mPAP [30,31]. Based on the mPAP measured through TTE, the patients were then classified into no PH (mPAP≤20 mm Hg at rest), borderline PH (mPAP>20 and <25 mmHg at rest), and PH (mPAP≥25).

Statistics

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 23) (IBM, Armonk, NY, USA). Mean ± standard deviation was used as a measure of central tendency. Statistical tool 'Compare means' was used to calculate mean ± standard deviation (SD) and the analysis of variance table was used to find out the statistical significance. Cross-tabulation was used to display data breakdown between two categorical variables, and Pearson's Chi-Square was used to find out statistical significance. A logistic regression test was applied to analyze the cause-and-effect relationship of continuous parameters [age and duration of silica exposure (DSE)] with prevalence of PH. In this

study, a p-value less than 0.05 was considered significant with either a negative or positive correlation on account of biological variability.

Results

The baseline characteristics of the study sample are shown in Table 1. The overall prevalence of PH among chronic simple silicosis patients was 25% (26/104) (Table 2). PH prevalence was 29.6% among SS while 20% among InS (p=0.52). PH prevalence was 34.2% among drillers and 19.1% among dressers (p=0.024). Table 3 shows nearby values of mean age and mean DSE among the SS group and InS group, with lower mean age among drillers than dressers, and lesser mean DSE among drillers than dressers, but statistical analysis failed to establish a significant association. Table 4 shows the logistic regression analysis of PH prevalence

Table 1. Baseline characteristics of the study sample.

Characteristics	Study sample	Significant smokers	Insignificant smokers	Drillers	Dressers
Number of patients, n	104	54	50	41	63
Age (mean±SD)	47.1±9.9	50.9±8.1	42.9±10.3	43.7±10.5	49.3±9.1
DSE (mean±SD)	21.3±8.6	24.1±7.7	18.22±8.5	17.7±7.5	23.2±8.1

SD, standard deviation; DSE, duration of silica exposure.

Table 2. Prevalence of pulmonary hypertension measured by transthoracic echocardiography.

TTE finding	Study sample	Smoking exposure		Occupation	
		Significant smokers	Insignificant smokers	Drillers	Dressers
Normal (%)	42 (40.4)	20	22	10	32
Borderline (%)	36 (34.6)	18	18	17	19
PH (%)	26 (25)	16	10	14	12
Total, n (%)	104	54 (51.9)	50 (48.1)	41 (39.4)	63 (60.6)
Prevalence percentage	25	29.6	20	34.2	19.1
		Value df p		Value df p	
Pearson Chi-square		1.33 2 0.52		7.47 2 0.024	

TTE, transthoracic echocardiography; PH, pulmonary hypertension; df, degree of freedom.

Table 3. Comparison of mean age and mean duration of silica exposure of pulmonary hypertension patients in smoking history-based groups and occupation type-based groups.

Parameter	Study sample	Significant smokers (n=16)	Insignificant smokers (n=10)	p	Drillers (n=14)	Dressers (n=12)	p
Age (mean±SD)	50.4±9.7	50.6±8.6	50.1±11.7	0.896	47.9±9.3	53.3±9.7	0.160
DSE (mean±SD)	24.9±8.3	24.75±8.2	25.1±8.9	0.920	22.3±8.7	27.9±7.1	0.086

SD, standard deviation; DSE, duration of silica exposure.

Table 4. Logistic regression analysis.

Outcome *vs.* Input	Model fitting criteria -2 log likelihood	Likelihood ratio tests Chi-square	df	p
Study sample (n=104)				
PH prevalence *vs.* age	45.185	90.465	68	0.036
PH prevalence *vs.* DSE	47.477	80.645	56	0.017
Significant smokers (n=54)				
PH prevalence *vs.* age	23.621	55.482	38	0.033
PH prevalence *vs.* DSE	21.315	58.339	46	0.105
Insignificant smokers (n=50)				
PH prevalence *vs.* age	16.372	63.480	58	0.289
PH prevalence *vs.* DSE	20.556	54.644	44	0.131
Drillers (n=41)				
PH prevalence *vs.* age	9.835	64.644	46	0.036
PH prevalence *vs.* DSE	13.801	50.585	38	0.083
Dressers (n=63)				
PH prevalence *vs.* age	21.633	66.036	50	0.064
PH prevalence *vs.* DSE	23.279	58.881	48	0.135

PH, pulmonary hypertension; DSE, duration of silica exposure; df, degree of freedom.

against age and DSE among the study sample, smoking history-based groups, and occupation type-based groups. It shows a significant association of PH prevalence with higher age in the study sample, the SS group, and the drillers group. A significant association of PH prevalence with longer DSE was only seen in the study sample. Table 5 shows a significant association of the SS-driller group with PH prevalence on comparison of echocardiographic findings with combined smoking history and occupation type-based groups.

Discussion

In this study, the overall prevalence of PH in chronic simple silicosis patients was 25% (26/104). However, most of the patients had mild PH (23/26) and only three patients had moderate PH (mPAP≥35 and <45). In the literature search in major databases regarding the prevalence of PH in silicosis or coal workers' pneumoconiosis or occupational lung diseases, we have not found any study for comparison of our results. While a large number of studies are available on the prevalence of PH among chronic obstructive pulmonary disease (COPD) and interstitial lung diseases. Liu *et al*. found that high-level silica exposure increased mortality from pulmonary heart disease [32]. As COPD and silicosis individually have a known tendency to cause chronic hypoxia, hence eventually leading to the development of PH, the study sample was further grouped based on smoking history to find the effect of smoking among these patients. Out of 104 study subjects, 54 had significant smoking history (10 or above pack years) and 50 had below 10 pack years of smoking history. PH prevalence was found to be higher among the SS group with 29.6% (16/54) against 20% (10/50) among the InS group (p=0.52), thus, showing a combined detrimental effect of smoking and silicosis in these subjects, but failing to show a significant difference statistically. Mean age (50.6 years in SS *vs*. 50.1 years in InS) and mean DSE (24.75 years in SS *vs*. 25.1 years in InS) were comparatively similar in PH patients of both groups. These findings are suggestive of a complex interplay of silicosis and smoking in these subjects. Ophir *et al*. analyzed the effect of smoking in artificial stone workers (n=100) and reported a protective effect of smoking in proven silicosis on pulmonary function test parameters [33]. Similarly, Tse *et al*. found that workers with silicosis were associated with an increased risk of mortality due to respiratory diseases (*i.e*., lung cancer, COPD, silicosis), with a relatively stronger risk ratio effect of silicosis in never smokers [34]. While studies conducted by Hessel *et al*. and Liu *et al*. have shown a combined detrimental effect of silicosis and smoking [35,36].

The mean age of presentation and mean duration of exposure were lower for drillers than dressers, as drillers being involved in machine-based mining activity, generating smaller sized and higher concentrations of RCS, have an increased risk of developing silicosis and PH than dressers who are involved in only manual work like chiseling or dressing the stone.

Workers exposed to silica dust are commonly screened based on respiratory symptoms, spirometry, and radiographic changes. However, even on radiological confirmation of having silicosis, cardiac evaluation is not routinely considered in the initial work-up and most of the time development of clinical manifestations of heart failure warrants cardiac evaluation. This leads to delayed diagnosis of cardiac manifestation secondary to silicosis when irreversible pathological changes in the heart have ensued.

At the 6th World Symposium on Pulmonary Hypertension, it was proposed that the mPAP threshold used to define PH should be lowered from 25 mmHg or above to 20 mmHg. As an mPAP above the upper limit of normal (above 20 mmHg) but below 25 mmHg is associated with an increased risk of morbidity and mortality compared with a normal mPAP, early identification of patients in this group is important to enable close monitoring and timely treatment initiation once clinically indicated [22]. In this study, there were 36 subjects diagnosed with borderline PH. On calculating PH prevalence according to this new definition, the prevalence of PH in our study would be increased to 59.6% (62/104). Silicosis results in permanent and progressive damage to the lung parenchymal even after stopping exposure to silica dust, which eventually leads to chronic hypoxia. Therefore, subjects with borderline PH (older definition) will eventually develop overt PH. Therefore, we also agree with this recommendation of lowering the mPAP threshold used to define PH from ≥25 mmHg to >20 mmHg.

Limitations of the study

The sample size of this study was small as exclusively chronic simple silicosis patients with no other clinico-radiological manifestations were selected. Statistical analysis may not have given results that can be extrapolated to the population. Data regarding the size and concentration of silica particles to which study subjects were exposed could not be collected. Also, various on-site preventive measures used by these subjects to control silica exposure were not included in this study. RHC is the gold standard to confirm PH diagnosis, but being an invasive and costly procedure, it was not used in this study to confirm PH.

Conclusions

This study has shown that a significant percentage of silicosis patients had developed PH in chronic simple silicosis along with varying statistical results for association with factors such as

Table 5. Comparison between echocardiographic findings and combined smoking-occupation-based groups.

	PH	Borderline PH	Normal	Prevalence (%)
SS-driller	10	10	0	50 (10/20)
SS-dresser	6	11	17	17.6 (6/34)
InS-driller	4	10	7	19.1 (4/21)
InS-dresser	6	10	13	20.7 (6/29)
Total	26	41	37	25 (26/104)
	Value	df	p	
Pearson Chi-Square	17.6	6	0.007	

PH, pulmonary hypertension; SS, significant smoker; InS, insignificant smoker; df, degree of freedom.

smoking, occupation type, age, and DSE, requiring large sample size based in-depth molecular and genetic studies to understand the exact role of various factors in silicosis pathogenesis. Lastly, we propose to include TTE in the initial work-up as a screening tool with a high benefit-cost ratio for early detection of PH in silicosis patients, thereby allowing timely interventions to reduce the severity of disability and improving quality of life.

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