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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 potential for permanent physical disability and increased socio-economic burden. Pulmonary hypertension (PH) secondary to chronic respiratory diseases signifies 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) on the basis of ≥ 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 versus 20% (10/50) among InS group (.52) ; and 34.2% (14/41) among drillers versus 19.1% (12/63) among dressers (p=.024). Mean age and mean duration of silica exposure 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=.007) with SS-driller group on 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.

Key words: pulmonary hypertension, chronic simple silicosis, transthoracic echocardiography.

Introduction

Silicosis is a fibrotic disease of the lungs attributable to the occupational inhalation, retention, and pulmonary reaction to respirable crystalline silica (RCS), usually as quartz and other crystalline forms (cristobalite and tridymite) [1,2]. Silica is found in 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 on the basis of 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 labors on the basis of 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]. Western part of Rajasthan has large number of workers engaged in sandstone mines with prevalence of silicosis in Jodhpur quarry workers is 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 manifestation of chronic hypoxia secondary to chronic respiratory disorders [20]. PH is defined by mean pulmonary artery pressure (mPAP) \geq 25mmhg at rest measured by right heart catheterization (RHC) [21]. At the 6th World Symposium on PH, 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 on basis of history, clinical evaluation, radiology and spirometry while cardiac assessment is mostly ignored especially in patients with early stages of disease while the presence of pulmonary hypertension in these patients worsens the prognosis [23].

The symptoms of pulmonary hypertension 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 as gold standard for diagnosis of PH but being invasive technique and having high cost, it cannot be used as screening tool. Trans-thoracic echocardiography (TTE) is non-invasive, cheaper and easily available investigation which qualifies as best screening tool for assessment of PH in suspected patients [28]. In this study, TTE screening of chronic simple silicosis patients was done to determine prevalence of PH. Secondary objectives were to correlate PH prevalence with smoking history, occupation type, age and duration of exposure.

Materials and Methods

Study centre

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

Study design

This was a cross sectional analytical study to estimate prevalence of pulmonary hypertension in chronic simple silicosis patients through transthoracic echocardiography. Study was approved by 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 inpatient or attending the outpatient clinic of the Department of Pulmonary Medicine, who had 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 basis of history of silica exposure and postero-anterior (PA view) chest radiographs compared with International Labor Office classification of radiographs of pneumoconiosis by a team of two pulmonologists and one radiologist to find out patients with nodular opacities of less than 10mm (ILO category P,Q,R) consistent with diagnosis of chronic simple silicosis. Six patients were excluded on screening because their radiographs were not fulfilling criteria for chronic simple silicosis. Remaining patients (n=104) were further evaluated with detailed history especially regarding smoking, type of occupation, age and duration of exposure. Therefore, study sample was divided into two groups: significant smokers (SS) with smoking history equal or above 10 pack years and insignificant smokers (InS) with smoking history below 10 pack years (Significant smokers and insignificant smokers 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 of 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 (cerebro-vascular 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 trans-thoracic echocardiography 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 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 \leq 20 mm Hg at rest), borderline PH (mPAP > 20 and < 25 mmHg at rest), PH (mPAP \geq 25).

Statistics

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 23). Mean ± standard deviation was used as measure of central tendency. Statistical tool 'Compare means' was used to calculate mean ± standard deviation (SD) and ANOVA table was used to find out 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. Logistic regression test was applied for analyzing cause and effect relationship of continuous parameters (age and DSE) with prevalence of PH. In this study, p value less than .05 was considered as significant with either 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 significant smokers while 20% among insignificant smokers (p=.52). PH prevalence was 34.2% among drillers and 19.1 % among dressers (p=.024). Table 3 shows nearby values of mean age and mean duration of silica exposure among SS group and InS group while lower mean age among drillers than dressers and lesser mean DSE among drillers than dressers, but statistical analysis failed to establish significant association. Table 4 shows logistic regression analysis of PH prevalence against age and duration of silica exposure among study sample, smoking history based groups and occupation type based groups. It shows significant association of PH prevalence with longer duration of silica exposure was only seen in the study sample. Table 5 shows significant association of SS-driller group with PH prevalence on comparison of echocardiographic findings with combined smoking history and occupation type based groups.

Discussion

In this study, overall prevalence of pulmonary hypertension 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 \geq 35 and < 45). On literature search in major databases regarding 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 large number of studies is available on prevalence of PH among chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILDs). Liu Y et al found that high-level silica exposure increased mortality from pulmonary heart disease [32]. As COPD and silicosis individually have known tendency to cause chronic hypoxia and hence eventually leading to development of PH, therefore study sample was further grouped on the basis of smoking history to find 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. Prevalence of PH was found to be more among SS group with 29.6% (16/54) against 20% (10/50) among InS group (p=.52). Thus showing combined detrimental effect of smoking and silicosis in these subjects but fail to show significant difference statistically. Mean age (50.6 years in SS vs. 50.1 years in InS) and mean duration of silica exposure (24.75 years in SS vs. 25.1 years in InS) were comparatively similar in PH patients of both the groups. These findings are suggestive of complex interplay of silicosis and smoking in these subjects. Noa Ophir et al analyzed effect of smoking in artificial stone workers (n=100) and reported protective effect of smoking in proved silicosis on pulmonary function test parameters [33]. Similarly, Tse LA 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 PA et al and Liu Y et al have shown combined detrimental effect of silicosis and smoking [35,36].

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 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 on the basis of respiratory symptoms, spirometry and radiographic changes. However, even on radiological confirmation of having silicosis, cardiac evaluation is not routinely considered in initial work-up and most of the times 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 heart have been ensued.

At the 6th World Symposium on PH, it was proposed that the mPAP threshold used to define PH should be lowered from 25 mmHg or above to above 20 mmHg. As an mPAP above the upper limit of normal (above 20 mmHg) but below 25 mmHg is associated with 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 as borderline PH. On calculating PH prevalence according to this new definition, prevalence of PH in our study would be increased to 59.6 % (62/104). Silicosis results in permanent and progressive damage to 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 mPAP threshold used to define PH from ≥25 mmHg to >20 mmHg.

Limitation of the study

Sample size was small in this study 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 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 invasive and costly procedure, it was not used in this study to confirm PH.

Conclusions

This study has shown that significant percentage of silicosis patients had developed PH in chronic simple silicosis along with varying statistical results for association with factors such as smoking, occupation type, age and DSE; requiring large sample size based in-depth molecular and genetic studies to understand exact role of various factors in silicosis pathogenesis. Lastly, we propose to include TTE in initial work-up as screening tool with high benefit-cost ratio for early detection of PH in silicosis patients, thereby, allowing timely interventions to reduce the severity of disability thereby improving quality of life.

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Characteristics	Study sample	Significant smokers	Insignificant smokers	Drillers	Dressers	
Number of	104	54	50	41	63	
patients, n	104	54	50	41	03	
Age (Mean ±	47.1±9.9	50.9±8.1	42.9±10.3	43.7±10.5	49.3±9.1	
SD)	47.1±3.3	50.5±0.1	42.9±10.9	49.7 ±10.9	+9.9±9.1	
DSE (Mean ±	21.3±8.6	24.1±7.7	18.22±8.5	17.7±7.5	23.2±8.1	
SD)	21.3±0.0	2 ±/ ./	10.22±0.5	.,., ., .,.,	23.2±0.1	

Table 1. Baseline characteristics of study sample.

SD – standard deviation, DSE – duration of silica exposure

TTE Study		Smoking Exposure			Occupation		
finding	sample	Significant smokers		gnificant nokers	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	104	54 (51.9%)	50 (48.1%)		41 (39.4%)		63 (60.6%)
Prevalence percentage	25%	29.6%	20%		34.2%		19.1%
Pearson Chi-Square		Value	df	p value	Value	df	p value
		1.33	2	.52	7.47	2	.024

 Table 2. Prevalence of PH measured by transthoracic echocardiography.

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

Table 3. Comparison of mean age and mean duration of silica exposure of PH patientsin smoking history based groups and occupation type based groups.

Parameter	Study sample	Significant smokers (16)	Insignificant smokers (10)	p value	Drillers (N=14)	Dressers (N=12)	p value
Age (Mean±SD)	50.4±9.7	50.6±8.6	50.1±11.7	.896	47.9 9.3	53.3 9.7	.160
DSE (Mean±SD)	24.9±8.3	24.75±8.2	25.1±8.9	.920	22.3 8.7	27.9 7.1	.086

SD, standard deviation; DSE, duration of silica exposure; p value, probability value.

Outcomo va Innut	Model fitting criteria	Likelihood ratio tests			
Outcome vs. Input	-2 Log Likelihood	Chi-square	df	p value	
Study sample (n=104)				I	
PH prevalence vs. Age	45.185	90.465	68	.036	
PH prevalence vs. DSE	47.477	80.645	56	.017	
Significant smokers (n=54)		I		I	
PH prevalence vs. Age	23.621	55.482	38	.033	
PH prevalence vs. DSE	21.315	58.339	46	.105	
Insignificant smokers (n=50	0)	1	I	I	
PH prevalence vs. Age	16.372	63.480 58		.289	
PH prevalence vs. DSE	20.556	54.644 44		.131	
Drillers (n=41)		1	I	I	
PH prevalence vs. Age	9.835	64.644	46	.036	
PH prevalence vs. DSE	13.801	50.585	38	.083	
Dressers (n=63)		I	I	I	
PH prevalence vs. Age	21.633	66.036	50	.064	
PH prevalence vs. DSE	23.279	58.881	48	.135	

Table 4. Logistic regression analysis.

Vs, versus; PH, pulmonary hypertension; DSE, duration of silica exposure; df, degree of freedom; p value, probability value.

	РН	Borderline	Norma	Prevalence
	F I I	PH	NOIMA	percentage
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 value
Pearson Chi-Square	17.6		6	.007

Table 5. Comparison between echocardiographic finding and combined smokingoccupation based groups.

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