Original Article

Cardiovascular complications in patients with interstitial lung disease and their correlation with 6-minute walk test and spirometry: A single-center study

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Abstract

Introduction: Pulmonary hypertension and other cardiac complications occur frequently due to chronic hypoxia induced by interstitial lung diseases (ILD) or due to connective tissue disorder itself. Two-dimensional (2D) echocardiography is ideal for identifying abnormalities at a given time. In this study, we tried to detect cardiovascular complications in patients with ILD using 2D echocardiography and correlate them with a 6-minute walk test (6 MWT) and spirometry. **Materials and Methods:** This study was carried out for 18 months including 100 consecutive cases of ILD. The diagnosis was made using the latest criteria as per the disease and high-resolution computed tomography (HRCT) thorax. All patients were evaluated with 2D echocardiography, 6 MWT, and spirometry along with routine investigations. Their results were analyzed using STATA 15.1 software. **Result:** Cardiovascular involvement was detected in 68% of cases. Pulmonary hypertension predominated with a prevalence of 50%. In spirometry, mean Forced expiratory volume in first second (FEV_1)and Forced vital capacity (FVC) were found to be 54.96 (L) and 53.49 (L), respectively, with a predominant restrictive pattern (89%). There was a significant correlation between baseline saturation of oxygen (SpO_2) and pulmonary arterial systolic pressure (PASP) with a *P* value of <0.05. Baseline SpO_2 and distance covered in 6 MWT had a significant correlation ($P = 0.014$). **Conclusion:** A baseline or nighttime hypoxia is responsible for developing PAH. Pulmonary arterial hypertension should be suspected in patients unable to perform 6 MWT or having low baseline SpO_2. A routine follow-up with a 6 MWT and baseline SpO_2 should be performed in each visit to identify early deterioration of the disease.

Keywords: 2D echocardiography, 6-minute walk test, interstitial lung disease, spirometry

Introduction

Interstitial lung disease (ILD) is a rare chronic progressive disease resulting from inflammatory infiltration of the interstitium or capillary endothelium of the lungs. Almost all patients develop some complications due to disease or therapy. These complications have been divided into pulmonary and extrapulmonary. Cardiac complications are the commonest extrapulmonary complications. Pulmonary artery hypertension (PAH) and other cardiac complications occur frequently due to chronic hypoxia induced by ILD or due to connective tissue disorder itself. Wang *et al.*[1] reported cardiovascular involvement in 64.7% of cases of connective tissue disease-associated ILD (CTD-ILD). In this study, myocardial functional limitations were found to have a prevalence of 42.4%, followed by valvular diseases (25.2%). In another study done by Schwarzkopf *et al.*,[2] it was found that 52.6% of patients were on treatment for cardiovascular involvement.

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The injury to the alveolar interstitium and capillary endothelium, which causes increased alveolar permeability and fibroblastic proliferation, is the main mechanism of the entire pathological process. A repeated insult causes excessive collagen deposition and fibrosis of the interstitium with or without capillary endothelium involvement. Due to pulmonary reserve, similar signs and symptoms as respiratory ailments and early cardiovascular complications remain masked. A study by du Bois *et al.*[3] showed that a decline of 50 m distance covered during a 6-minute walk test (6 MWT) over 24 weeks had an increased mortality risk of 4-fold within 1 year. Similarly, reduced Diffusing capacity of the Lungs for carbon monoxide(DLCO) and low 6 MWT oxygen saturation (SpO_2) are associated with poor survival in ILD patients with PAH.[4] In another study, it has been found that although desaturation on 6 MWT was not a predictor of PAH; it has a high negative predictive value in the prediction of ILD-associated PAH.[5] Even there have been attempts to use newer tests like incremental shuttle walk test (ISWT), a more effective alternative to 6 MWT for assessment of functional capacity in ILD-PAH.[6]

Although two-dimensional (2D) echocardiography is good for identifying abnormalities at a given time or rest only, the cardiac function and its relation with hypoxia cannot be measured. Thus, for physiological status, 6 MWT with SpO_2 monitoring and spirometry for functional assessment of lungs in ILD becomes an essential tool.

There are no studies available for the correlation between these three parameters together. So in this study, we tried to determine the cardiovascular complications in patients with ILD using 2D echocardiography and correlate them with 6 MWT and spirometry.

Rationale

Cardiovascular complications occur early in idiopathic pulmonary fibrosis(IPF) and other ILDs without any symptoms. So an early detection will be helpful in delaying progression and thus prevent functional limitations due to complications.

Materials and Methods

This study was conducted at the Department of Pulmonary Medicine, Department of Clinical Immunology and Rheumatology, and Department of Cardiology, Kalinga Institute of Medical Sciences. One hundred consecutive patients with ILD who attended the above OPD or IPD from August 2018 to May 2020 were included in the study. Patients with other lung diseases such as COPD, asthma, bronchiectasis, pulmonary tuberculosis, and underlying preexisting heart disease were excluded from the study.

For maintaining the universality of data collection, a proforma having sets of questionnaires related to clinical history, comorbidities, spirometry details, 6 MWT, 2D echocardiography, and routine blood investigations was used. Each patient was classified into five groups: idiopathic interstitial pneumonia (IIP), autoimmune ILDs, hypersensitivity pneumonitis (HP), sarcoidosis, and other ILDs. Later, these were again subclassified into various categories as per the recent classification of ILD.[7] A high-resolution computed tomography scan (HRCT) was used for identifying the radiological patterns and they were divided into patterns such as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), and cryptogenic organizing pneumonia (COP).[8,9] All patients were subjected to 2D echocardiography, pre and postbronchodilator spirometry, and 6 MWT. 2D echocardiography was done using Philips Imaging System epiq-7 by a cardiologist. Spirometry was done using WinspiroPRO 8.1® software and MIR minister computer-based spirometer. Pulmonary function test (PFT) was classified into restrictive, obstructive, and mixed patterns. Furthermore, severity classification is done using the same BTS guidelines.[10]

The 6 MWT was performed in a 100 m long hallway according to American Thoracic Society guidelines.[11] The 6 MWT was performed without oxygen in all patients. All patients with a baseline SpO_2 <90% were not taken up for the 6 MWT. This study was approved by the ethical committee of the Kalinga Institute of Medical Sciences, Ref. No. KIMS/KIIT/IEC/136/2018.

Statistical analysis

In this study, the continuous variables were presented as means (± SD). We expressed categorical variables as frequencies and percentages. The student's *t*-test was performed for comparing the means of two different groups. Nominal categorical data between the groups were compared using the Chi-square test or Fisher's exact test as appropriate. We compared the frequency of one categorical variable with different values of the second categorical variable. A value of $P < 0.05$ was considered statistically significant. The analysis was performed using STATA 15.1 software.

Results

In our study of 100 consecutive cases of ILD, we found six different causative factors for ILD, and these were grouped. The prevalence of IPF and systemic sclerosis-associated ILD (SSc-ILD) were 23%, followed by mixed connective tissue disease-associated ILD (MCTD-ILD) 20%, overlap CTD-ILD 13%, rheumatoid arthritis-associated ILD (RA-ILD) 11%, and undifferentiated CTD-associated ILD 10%.

There was a significantly higher prevalence of the disease among females than males (71% vs. 29%). A similar pattern was noticed in all subgroups of diseases including idiopathic ILD (12% vs. 11%), Overlap CTD-ILD (11% vs. 2%), MCTD-ILD (17% vs. 3%), RA-ILD (11% vs. 4%), systemic sclerosis-ILD (19% vs. 4%), and UCTD-ILD (5% vs, 5%), respectively.

The mean age of presentation for patients with CTD-ILD was 50.04 years. (±15.156 years). IPF group of patients had a late onset of disease (64.78 ± 9.733 years), whereas the MCTD group of patients had an earlier onset (38.55 ± 14.207 years).

Gastroesophageal reflux (GERD) was the commonest comorbidity reported followed by systemic hypertension, type-2 diabetes mellitus, and obesity. Pedal edema was seen in 33 cases, out of which 22 had raised PASP but 11 had normal PASP. Systemic hypertension was commonly observed in the IPF group followed by SSC-ILD and UCTD-ILD. Diabetes was observed most commonly in the IPF group followed by the UCTD-ILD group.

Echocardiographic evaluation: 68% of patients with ILD were found to have cardiac illness in some or the other forms. PAH was seen in 50% cases with mean PASP of 30.96 mmHg (SD-21.27, 95%; CI-26.74–35.18), tricuspid regurgitation was seen in 39%, concentric LVH in 19% cases, mitral regurgitation in 7%, pericardial effusion in 5%, aortic regurgitation in 5%, dilated left atrium in 4%, atrial fibrillation in 1%, and right ventricle dysfunction in 4%. The overlap CTD-ILD group had the highest mean PASP. [Tables 1 and 2]

Spirometry

Out of 93 patients who performed spirometry, 89 patients had a restrictive pattern, whereas four patients had a mixed pattern. The grading was performed as mild (grade 1), moderate (grade 2), moderately severe (grade 3), severe (grade 4), and very severe (grade 5).[7] Maximum cases had grade 3 and grade 4 levels of restriction on PFT (24% in each group). This was followed by 18% for grade-1, 14% for grade-2, and 13% for grade-5. Mean FEV_1 was found to be 54.96 (SD 50.97 to 58.94) (% predicted or 1.2887 SD1.1701 to 1.4073 L), FVC = 53.49 (SD 49.89 to 57.10) (% predicted or 1.5311 SD 1.3953 to 1.6669 L, FEV_1/FVC = 104.29 (SD 101.33 to 107.25) (%), which shows a clear predominance of restrictive pattern in our study.

6-minute walk test

A total of 18 patients were unable to perform 6 MWT due to baseline SpO_2 of less than 90% or having dyspnea at rest. Twenty-six patients were not able to complete the test due to excessive dyspnea or pain in the lower limbs. Fifty-six patients completed the 6 MWT. The mean distance completed in 6 min for patients who were able to complete the test was 382.55 m (±65.508 m). Twenty-six patients who stopped before completing 6 min were able to walk a mean distance of 128.73 m (±61.568 m).

Correlation between 2D echocardiographic study, 6 MWT, and spirometry: There was a significant correlation between baseline

Table 1: Showing echocardiographic parameters and their statistical significance with PASP

Echocardiographic parameters	PASP < 25 mmHg	PASP > 25 mmHg	*P*
Dilated right atrium (%)	1	13	0.0004
Dilated right ventricle (%)	1	14	0.0002
Tricuspid velocity (cm/s)	164.58±26.94	305.70±73.61	0.0001
Tricuspid gradient (mmHg)	11.22±3.25	39.62±19.69	0.0001
PASP (mmHg)	16.22±3.25	45.82±21.34	0.0001
Tricuspid regurgitation(%)	4	35	0.0001
Right heart failure (%)	0	14	0.0001
IVSDd (cm)	1.1967±0.2216	1.2596±0.9696	0.6598
IVSSs (cm)	1.52560±0.31108	1.57605±0.31458	0.4516
LVIDs (cm)	2.4523±0.5835	2.5598±0.5972	0.3728
LVIDd (cm)	4.0610±0.4704	3.9890±0.7036	0.5543
LA diameter (cm)	3.2470±0.4360	3.2509±0.5765	0.9732
Aortic root diameter (cm)	2.7181±0.5107	2.5068±0.4717	0.0585
LVPWs (cm)	1.5811±0.2281	1.4620±0.2303	0.0145
LVPWd (cm)	1.09680±0.17868	1.25068±0.96105	0.2884
Concentric LVH (%)	9	10	0.8012
Aortic regurgitation (%)	2	3	0.6503
Mitral regurgitation (%)	2	5	0.2440
Pericardial effusion (%)	3	2	0.6503
Atrial fibrillation (%)	1	0	

Table 2: Showing correlation of different variables in two different types of HRCT thorax patterns

Variables	UIP	NSIP	*P*
PASP (mmHg), mean ± SD	35.60±23.71	27.60±18.43	0.0659
TR velocity (cm/s), mean ± SD	253.19± 98.35	222.48±80.07	0.0941
SpO_2 at rest (%), mean ± SD	92.57±7.28	94.90±4.91	0.0667
Distance covered in 6 MWT (m), mean ± SD	268.61±130.39	332.73±133.24	0.0337
FVC (L), mean ± SD	1.4717± 0.6097	1.5411±0.6660	0.6109
Heart failure (*n*)	9	5	0.2534
Duration of disease (in month), mean ± SD	47.36±42.56	64.04±63.51	0.1345

SpO_2 and the distance covered in 6 MWT ($P = 0.014$). Post 6 MWT, SpO_2, and distance covered in 6 min also had a significant correlation with a P value of 0.049.

There was a significant correlation between baseline SpO_2 and pulmonary artery systolic pressure (PASP), with a P value of 0.000. However, there was no significant correlation between the distance covered in 6 MWT and PASP ($P = 0.366$).

There was no significant correlation between a patient who could not complete 6 MWT and those who completed the test ($P = 0.273$). There was a significant correlation between pre-6 MWT SpO_2 (baseline SpO_2) and post-6 MWT SpO_2 ($P = 0.003$). In our study, we found a significant correlation between the baseline SpO_2 and SpO_2 measured after a 6 MWT ($P = 0.003$).

Discussion

In our study among CTD-ILD cases, we found SSc-associated ILD had the highest prevalence. A total of 68% of our patients were found to have a cardiac illness by 2D echocardiography done by the transthoracic method. We found raised mPASP in 50% of cases followed by tricuspid regurgitation in 39% of cases. Although there are multiple methods and associated findings that are required for identifying PAH, we have used mPASP as the single most important determinant marker for PAH. Age and obesity are two confounding variables that can increase the PASP significantly.[12,13] But as the mean age of incidence was around 63 years in our study, a comparison of age-wise PASP could not be done. Obesity was seen in only six patients and two (33.3%) of them had normal mPASP. There is very little chance of the "age" factor producing high PASP.

Concentric LVH was seen in 19% of cases of which 7% of patients had hypertension at rest and the remaining 12% were normotensive. Mitral regurgitation was seen in 7% of cases. Pericardial effusion was seen in 5% of cases, the maximum of which was seen in the non-IPF group. MCTD and systemic sclerosis are two main CTD groups in which pericardial effusion has been reported mainly, which is again consistent with our study.[14] Other findings were dilated left atrium in 4%, right ventricular dysfunction in 4%, and atrial fibrillation in 1% of cases. Interventricular septal thickness (IvSD) was 1.2596 ± 0.9696 cm in patients having PAH, whereas in patients without PAH, it was 1.1967 ± 0.2216 cm. Both of the values are greater in comparison with the normal range (0.83 cm to 1.12 cm) of interventricular septal thickness.[15] Hypertension in ILD can increase in the thickness of the interventricular septum. Aortic root diameter dilation was more in patients having normal mPASP than those having mPASP >25 mmHg. There are various causes of aortic root dilation in which idiopathic, inflammatory disorders, and hypertension are important and share the same multifactorial causative factors as ILD.[16]

Usually, IPF patients with cardiovascular changes have a much rapid course in comparison with CTD-induced ILD cases.[12] However, in our study, we found that mPASP is much higher in overlap CTD-associated ILD, followed by SSc-associated ILD and MCTD-associated ILD. The rise in mPASP in CTD-ILD cases can be attributed to a long survival period and less severe course of the disease itself in contrast to the IPF group.

In our study, 7% could not perform spirometry due to baseline dyspnea of mMRC scale grade 4. Out of 93% of cases, 89% had a restrictive pattern and 4% had mixed patterns. After comparing we found a significant correlation between raised mPAP and grade of dyspnea. A decrease in mPASP of patients having a grade 5 level of respiratory limitation could be justified by ongoing treatment with pulmonary vasodilator therapies or drugs reducing preloads or less number of survivors at this stage of the disease.

A total of 18 patients could not perform 6 MWT, out of which 17 had severe dyspnea at rest and one patient had a severe joint deformity. A 6 MWT not only depends on the respiratory system but also on the cardiovascular and neuromuscular system.[17] It identifies the severity of the disease and its impact on individual performance,[18] whereas HRCT and PFT are unable to access individual functional limitations. Thus, a 6 MWT becomes a necessary tool for its reliability and ease of performing. In our study, we have found a mean value of 382.55 ± 65.508 m for patients who were able to complete, whereas patients who stopped before 6-min due to any reason were able to walk only 128.73 ± 61.568 m, which is lower than the reported normal values in healthy adults (400 m to 700 m).[19]

As per the ESC/ERS guidelines, a 6-minute walk distance (6 MWD) of more than 500 m indicates a good prognosis whereas, a distance of less than 300 m indicates a poor prognosis.[20] In our study, we observed that there are high discrepancies between severities of PAH and distance covered in a 6-MWT. It indicates only PAH severity cannot be taken as a single independent factor for severity assessment of functional limitations in ILD ($P = 0.366$). Certain other studies have shown that pulmonary hemodynamic parameters, cardiac markers, quality of life parameters, and their relationship with exercise capacity are variable.[21,22] According to a study by Gaine *et al.*, there are limitations of 6 MWD; the sensitivity of 6 MWD is low in patients with milder symptoms who can walk longer and there is reduced adequacy in patients under PAH treatment.[23] This ceiling effect in 6 MWD may mask the efficacy in patients who have longer walking distance at baseline with significant pathology, as has been found in a study by Bosentan in functional class II patients.[24] Again it is difficult to determine the changes in the walking distance among patients with a higher 6 MWD of 450 m or more; in some patients, 6 MWD is higher with severe hemodynamic changes at the time of PAH diagnosis.[25]

Finally, in a developing country like India, in the resource-poor settings where the role of a family physician is of paramount importance, simple bedside/home test tools such as 6 MWT and pulse oxymeter for SpO_2 along with spirometry can be of

immense value to detect pulmonary arterial hypertension early in patients with interstitial lung disease. Early detection of PAH in ILD and its treatment can prevent morbidity and mortality in these patients. Although our study having limitations like small sample size, single-center study; these findings still could provide simple and reliable tools like 6 MWT and spirometry as invaluable tools for early detection of PAD in ILD patients.

Conclusion

There is a significant correlation between baseline hypoxia and raised PASP that suggests a baseline or night time hypoxia as an eminent factor for developing PAH. There is a significant correlation between distances covered in 6 MWT, mPASP, and baseline SpO_2. Using this observation, we can suspect pulmonary arterial hypertension in patients who are unable to perform 6 MWT or having low baseline SpO_2. A routine follow-up with a 6 MWT and baseline SpO_2 should be done in each visit to identify early detection of PAH in patients with ILD.

Key points

1. Pulmonary arterial hypertension (PAH) in interstitial lung disease (ILD) is an important cause of mortality.
2. 6-minute walk test (6 MWT) and spirometry at every visit are simple tools for early detection of PAH in ILD patients even in primary care settings.

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Conflicts of interest

There are no conflicts of interest.

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