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Original Research Article

A PROSPECTIVE STUDY OF THE CORRELATION BETWEEN DIFFUSING CAPACITY OF THE LUNG FOR CARBON MONOXIDE (DLCO) AND HIGH-RESOLUTION COMPUTED TOMOGRAPHY IN THE FOLLOW UP OF DIFFUSE PARENCHYMAL LUNG DISEASES

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ABSTRACT

Background: Diffuse parenchymal lung diseases (DPLD) refer to a group of lung diseases affecting the interstitium. Diffusing capacity lung for carbon monoxide (DLCO) is a sensitive indicator of gas exchange & it is abnormal in patients with interstitial lung diseases. Pulmonary function studies like DLCO and FVC may help in the prognostic evaluation of these conditions. **Aim:** To assess the strength of correlation of DLCO in a suspected case of DPLD with suggestive HRCT pattern and to evaluate the potential of DLCO in assessing the extent and severity grading of HRCT diagnosed idiopathic pulmonary fibrosis subset. **Materials and Methods:** All patients who came to the outpatient department with a clinical and HRCT diagnosis of DPLD were included in the study. A detailed history and examination were done in all these patients and DLCO was done. Patients were followed up at 6 months and 1year following the diagnosis with repeat DLCO. A repeat HRCT was done at 1 year follow up. **Result:** Our study had 32 patients (49.2%) with a diagnosis of Idiopathic pulmonary fibrosis followed by sarcoidosis (9.2%), nonspecific interstitial pneumonias (9.2%) and hypersensitivity pneumonitis (9.2%). The relation between DLCO grade and HRCT score at presentation as well as at the end of first year showed a good positive correlation. **Conclusion:** The present study detected a strong positive correlation between impairment in DLCO with HRCT findings in DPLD patients. A serial monitoring of DLCO showed that the changes over time parallels with the findings in HRCT. Hence DLCO can be recommended for prognostic evaluation & serial assessment of DLCO will help in follow up of IPF patients.

INTRODUCTION

Diffuse parenchymal lung diseases (DPLD) are a heterogeneous group of diseases characterized by damage to the lung parenchyma arising from the effects of inflammation and fibrosis.[1] The term ‘‘interstitial lung disease’’ is synonymous with ‘‘diffuse parenchymal lung disease’’, while the latter was used in the 1999 BTS guideline, a decision was made to adopt the term interstitial lung disease (ILD).[2] While the interstitium is the primary site of injury in ILD, other regions like the air spaces, peripheral airways and vessels are also commonly involved.[1,3] Pulmonary interstitium comprises of the region between alveolar epithelium and pulmonary vascular endothelium. The term DPLD describes many entities that injure the lung parenchyma, producing a disease with similar clinical, radiographic and physiologic features.

Even though there are many causes of ILD, interstitial pulmonary fibrosis (IPF) is the most common form of ILD and certainly the most serious. IPF is characterized by an inexorable progression of interstitial pulmonary fibrosis that results in a restrictive lung disease and worsening of gas exchange. By definition, IPF is a usual interstitial pneumonia, in the absence of a cause or an explanation.

Diffusing capacity lung for carbon monoxide (DLCO) is a sensitive indicator of gas exchange and it is abnormal in patients with interstitial lung diseases. Pulmonary function studies like DLCO and forced vital capacity (FVC) may help in the prognostic evaluation of these conditions.

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Though open lung biopsy is considered as the gold standard for the diagnosis of ILD, typical high resolution computerized tomography scan (HRCT) patterns can aid in diagnosis, in those who are unable to undergo a surgical biopsy procedure. Several studies have shown that HRCT patterns closely relate with certain pulmonary function studies like DLCO and FVC, and may help in prognostic evaluation. Hence, we proceeded with this study for finding the strength of association between the disease extent, severity and progression of ILD with DLCO in relation to HRCT pattern which is the current non-invasive gold standard for diagnosing DPLDs.

Aim

The primary aim was to assess the strength of correlation of DLCO with HRCT pattern, in a suspected case of ILD. The secondary aim was to evaluate the potential of DLCO in assessing the extent and severity of HRCT diagnosed idiopathic pulmonary fibrosis and its role in prognostic evaluation on follow up.

MATERIALS AND METHODS

A prospective, observational study was conducted at the Pulmonology department in a tertiary care teaching hospital for a period of 18 months. All patients who came to outpatient department (OPD) of our department with a clinical and HRCT diagnosis of DPLD and who gave consent for follow up evaluation were included in the study. All patients diagnosed as DPLD were evaluated with baseline investigations, HRCT and DLCO and were followed up. A convenience sampling method was adopted and a total of 65 patients were enrolled for the study. The patients who had concurrent emphysema, advanced pulmonary hypertension and incomplete functional data were excluded from the study.

After obtaining approval from the institutional research committee and institutional ethics committee and after getting informed consent, eligible patients were interviewed. A detailed history with reference to the locality of stay, proximity to industrial firms, history of any long-term diseases/medications, family history of any illness, history of occupational exposure to any specific agent was recorded and physical examination performed in all patients at the time of initial presentation. Laboratory investigations included hemogram, autoantibody screening for connective tissue diseases, chest radiography and spirometry. In selected patients bronchoalveolar lavage studies and transbronchial lung biopsy were performed.

All patients underwent a HRCT thorax. An assessment of disease extent and severity in HRCT thorax was done based on a scoring system published by Warrick et al (4). Different abnormalities corresponding to increasingly severe disease are given increasingly high scores. All these patients with an HRCT were evaluated with a DLCO test using the machine Quark PFT module, COSMED (single breath method using methane as tracer gas) within 2 months of the scan. DLCO test was performed as per the recommendations of ATS/ERS consensus. The reported DLCO value was taken as the average of the first 2 tests that meet the reproducibility criteria, but if 5 tests were performed and no two tests meet the reproducibility criteria, the reported value was the average of the 2 tests with the highest inspiratory volumes. The disease severity was graded based on the DLCO values as follows.

Grading	Degree of Severity	DLCO, % Predicted
1	Mild	> 60 and less than lower limit of normal
2	Moderate	40-60
3	Severe	<40

The patients in the study group were treated based on their disease type as per the recommended guidelines. These patients were followed up at 6 months and 1 year following the diagnosis with repeat DLCO. A repeat HRCT was taken one year after the radiological diagnosis. The extent and severity of the disease in HRCT was correlated with the DLCO at 1 year following the diagnosis. The final score was then correlated to severity grading of DLCO.

Statistical analysis was done using SPSS software version 18. The correlation between the DLCO severity grades and the HRCT scores at presentation and at follow-ups were assessed. A Pearson correlation coefficient (r) was calculated for each. The degree of significance of these correlation coefficients values was calculated by obtaining the p value. A p value <0.05 is considered significant. The results were then analysed to validate the hypothesis.

RESULTS

A total of 65 patients who met the inclusion criteria were included in the study. The age group of the patients were between 36 years and 86 years with the mean age of 62 years. Majority of the patients were in the age group of 51–60 and 61–70 years, the number being 16 each (24.6%). Of the 65 patients, 43 (66.2%) patients were males and 22 (33.8%) were females. Female patients were more in the younger age group while the ratio was in favour of males in the upper age group. Regarding the different types of DPLDs in the study group, majority of the patients had a diagnosis of Idiopathic pulmonary fibrosis (49.2%). The other common types were Non-specific interstitial pneumonitis (NSIP), Hypersensitivity pneumonitis (HP) and Sarcoidosis.

The DLCO % predicted was calculated and the severity of DLCO was graded as described previously. Majority of the patients had a DLCO severity grading of 2 at presentation (63%). At the first follow-up after six months, 37 patients (56.9%) had a severity grade of 2 and 21 (32.3%) patients had a grade 3 severity. But when it came to the second follow-up, the number of patients with grade 2 and

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grade 3 severity were almost equal (31 and 30 patients respectively).

The HRCT global score was calculated from the severity score and extent score. At presentation the HRCT scores ranged from 10 to 26 with the mean score being 16.8. Majority of the patients had a score between 16-20 (36.9%) followed by 11-15(35.4%). Only one patient had a score above 25 (1.5%). At one year follow-up, 33.8% had score between 21-25 and 30.7% had a score 16-20.

Among the IPF patients in the study, 17 patients (53.1%) had a DLCO severity grade of 2 and 13 patients (40.6%) had a grade 3 severity. At first follow-up after six months, 18 patients (56.3%) had a severity grade 3 and 13 patients (40.6%) had a grade 2 severity DLCO. After one year, 26 patients (81.3%) had a grade 3 severity and 6 patients (18.7%) had a grade 2 severity.

Initially the correlation between the DLCO severity grades at presentation (DLCO grade P1) and the HRCT scores at presentation (HRCT score P1) were assessed. It gave a Correlation coefficient (r) = +0.665 with a p value <0.0001. Next, the correlation between the DLCO severity grades at second follow-up (DLCO grade R2) and the HRCT scores at the end of first year (HRCT score R2) were assessed. It had a Correlation coefficient (r) = +0.732 with p value <0.0001. Thus, both these groups showed a good positive correlation between the two parameters with a significant p value.

DISCUSSION

Our study had 65 patients with a diagnosis of ILD, the age group ranging from 36 years to 86 years. It was found that the male to female ratio was in favour of females in the younger age group but more male patients had ILDs than females as the age increased. According to a study by Rajkumar et al of the 289 ILD cases studied, there were 158 (54.68%) females.[5] Of the 32 patients with IPF, 27 patients (84.3%) were males and 5 patients (15.6%) were females. Thus, there was a marked increase in the male: female ratio when it came to IPF. In contrast to our study, a study by Maheshwari et al in 2004, showed a female preponderance of IPF and mean age of presentation about 50 years.[6] Maheshwari et al noted that Idiopathic pulmonary fibrosis prevalence increased with age, with most patients aged ⩾65 years. Even in our study it was observed that the prevalence of IPF was more in the age group of 71 – 80 years (34.3%).

Our study had 32 patients (49.2%) with Idiopathic pulmonary fibrosis followed by sarcoidosis (9.2%), nonspecific interstitial pneumonias (9.2%) and hypersensitivity pneumonitis (9.2%). In 1979, Jindal et al published their data on cases of DPLD seen over a period of five years and among them 46% of cases were having IPF.[7] In 1984, Sharma et al reported IPF to be present in 28.6% of their patients with DPLD.[8] In 2004 a group of investigators from south India supported the fact that secondary DPLD (55%) was more common than IPF. In 2010, Sen et al(68) in their retrospective analysis reported that besides IPF, sarcoidosis, ILDs secondary to CTD and hypersensitivity pneumonitis were the main diagnoses (9).

The DLCO is the most sensitive of the static pulmonary functional parameters, and may be reduced even when lung volumes are preserved (10). Several studies have demonstrated that six-to-twelve-month changes in FVC and DLCO values are highly predictive of outcome and become more predictive of prognosis over time than most baseline characteristics, including the histopathologic diagnosis. Clinically significant changes in FVC and DLCO have typically been considered greater than 10% and greater than 15%, respectively. Changes greater than 15% in DLCO were predictive of mortality risk(11).

In our study, the DLCO % predicted was calculated and the severity of DLCO was graded according to ATS/ERS consensus. Majority of the patients had a DLCO severity grading of 2 at presentation (63%) which meant a DLCO % of 40 - 60%. A grade 3 severity corresponding to DLCO % of < 40% was seen in 23% of patients at presentation. The first review was at 6 months and the patients were again assessed for DLCO % and were graded based on that. Even during the first follow-up, majority of the patients had a DLCO severity grading of 2 (56.9%) and 32.3% had a grade 3 severity. During the second follow-up at the end of first year, the number of patients with a grade 2 and grade 3 severity were almost equal (47.7% and 46.2% respectively).

Since HRCT is the radiological imaging technique that most closely reflects changes in lung structure, it is the method of choice for the diagnostic work-up of patients with known or suspected DPLD. At presentation majority of the patients had a HRCT severity score between 16 and 20 (36.9%) whereas at the end of first year 33.8% had HRCT severity score between 21 and 25. In the IPF group majority of the patients had a HRCT severity score between 16 and 20 (43.7%) whereas at the end of first year 56.3% had HRCT severity score between 21 and 25.

The correlation between the DLCO grades and HRCT scores were calculated in the study group at presentation and at the end of first year. In our study, both showed a good positive correlation with a significant p value. Since we have compared the correlation between DLCO grade and HRCT score instead of using DLCO % predicted, we got a positive correlation as opposed to other studies where the DLCO % and HRCT score was compared. Wells et al with the largest sample size so far studied, found DLCO % of predicted to correlate well with HRCT of patients without emphysema (r = −0.68) (12). Staples et al studied 23 patients and found DLCO to correlate well (r = −0.64) with HRCT (visual analogue scale of 0‑100%) (13). Study by Isaac et al has been able to demonstrate a better significance or

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a larger r value (r = −0.721) for correlation of DLCO % of predicted with HRCT (10). Thus, the results of this study are almost similar to other studies in the recent literature.

According to study by Isaac et al, although HRCT is the best non-invasive method for assessing the pattern (fibrosis versus inflammation) and quantifying the extent of the disease in idiopathic interstitial pneumonia patients at diagnosis, its frequent repetition is ill-advised because of the radiation burden and its high cost (10). This study showed that cough severity and dyspnoea severity among symptoms (smaller r value), FVC, TLC, DLCO among PFT parameters and lowest oxygen saturation from among the six-minute walk test have statistically significant correlation with total HRCT score in patients with idiopathic interstitial pneumonia. DLCO showed the best correlation and among the diffusion capacity measures of which DLCO corrected % of predicted correlated the best with HRCT. As per our study and other studies as mentioned DLCO% or grading correlate well with the HRCT severity grading during follow-ups in IPF patients. Thus, a periodic monitoring of DLCO% at follow-up eliminates the need to have frequent HRCT during further visits.

Absence of lung biopsy in certain cases for diagnosis of various DPLDs including IPF is a limitation of the present study. Only sixty-five patients satisfied the criteria for inclusion, which is a small number and hence may not represent the characteristics of DPLD patients in a large population. Presence of higher prevalence of IPF compared to other DPLDs in the present study may be due to selective referrals from periphery. In the present study the results obtained were based on HRCT findings, which represent a sensitive method for determining the extent of parenchymal alterations in ILD. HRCT allowed us to include ill patients who could not undergo an open lung biopsy. Thus, our study population is homogeneous and it can be considered representative of all the stages of the disease.

CONCLUSION

Management of DPLDs is always a challenge, but early diagnosis, appropriate treatment and a balanced prognostic evaluation are always rewarding. The present study detected a strong positive correlation between impairment in diffusion lung capacity for carbon monoxide with HRCT findings in DPLD patients. The present study also confirms a positive correlation between impairment in DLCO with HRCT severity and extent in patients with idiopathic pulmonary fibrosis. A serial monitoring of DLCO showed that the changes over time parallels with the findings in HRCT.

Hence DLCO can be recommended for prognostic evaluation and a serial assessment of DLCO will help in follow up of IPF patients. This can avoid the recommended repeat HRCT at 1 year following diagnosis thus reducing the economic as well as radiation burden to the patient.

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