Pulmonary function in patient with ulcerative colitis: A cross-sectional study from North India

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Abstract—Aim: To determine the type and frequency of pulmonary involvement in patients with UC and to determine the distribution of pulmonary dysfunction in patients with UC. Methods: A total of 39 cases of UC, were enrolled consecutively in this study from the Department of Gastroenterology. The age, sex, family history, duration of disease, biochemical parameters (CRP, ESR, blood routine test, etc.), lung function, chest X-ray, diagnoses, and treatments were collected. Patients and controls underwent standard pulmonary function testing. Comparisons of rates among multiple groups were done with Fisher exact test, continuous variables were compared with one-way ANOVA. Results: According to the true love index, the severity of active UC was moderate and severe among 36.7% and 63.3% of subjects respectively. The pulmonary function test “FCV” showed reduced mean FCV among subjects with active UC (2.86±0.77 litres) and inactive UC (3.91±0.62 litres) as compared to controls (4.04±1.14 litres). Among the patients with deranged PFT, 1 (7.6%) had obstructive, 7 (53.8%) had small airway disease and 5 (38.6%) had a restrictive pattern of lung involvement. Conclusion: Subclinical pulmonary dysfunction is frequent in UC and dependent on disease activity. Some alterations were sub-clinical and some of the patients showed troublesome pulmonary symptoms.
Keywords—Ulcerative colitis, pulmonary function, inflammatory bowel disease, obstructive lung disease, functional residual capacity

Introduction

Ulcerative colitis (UC) is a disease of unknown etiology, which occurs due to an abnormal immune response leading to chronic intestinal inflammation [1]. It is characterized by relapsing-remitting inflammation of the gastrointestinal tract. Nearly 50% of inflammatory bowel disease (IBD) patients will experience at least one extraintestinal manifestation [2]. Bronchopulmonary involvement is rare in IBD [3]. Airway disease of different types involves different parts of the bronchial tree from the glottis to small airways, leading to ventilation defects, bronchial hyperresponsiveness, and sputum or bronchoalveolar lavage lymphocytosis, as well as radiological and histological abnormalities [4].

Pulmonary involvement in UC was first reported in 1976 [5]. It is being increasingly reported in recent years. Pulmonary function test (PFT) abnormality in cases of UC has been reported to be 17–55% [6], which includes a decrease in the maximal mid-expiratory flow rate (MEFR), elevated functional residual capacity (FRC), decrease in the gas transfer factor [diffusion lung capacity for carbon monoxide (DLCO)], or increased frequency of bronchial hyperresponsiveness [7].

Respiratory abnormalities reported in cases of UC include obstructive lung disease, interstitial lung disease, small and large airway disorders, bronchitis, bronchiectasis, bronchiolitis obliterans, and an increase in bronchial responsiveness [8]. Most of these cases are overt or subclinical. However, most patients were found to have a normal chest X-ray [9]. Inflammatory bowel diseases, that is, Crohn's disease (CD) and UC, have a complex pathogenesis involving interaction between genetic, environmental, immune regulatory, and microbial factors. Disordered innate immunity also has a role to play. The structural similarity between the intestine and the bronchus and their common origin from the primitive foregut provide a basis for the development of inflammatory changes in the bronchus in patients with IBD [10,11].

The prevalence of pulmonary involvement in IBD has been varying in reports, and its clinical implication is not clear. However, pulmonary manifestations must be diagnosed and treated early, or else they will lead to irreversible damage to the airway wall or the end-stage lung disease. Occult pulmonary disease may be diagnosed using variables of the PFT. Hence, we undertook this study with the aim to determine the type and frequency of pulmonary involvement in patients with UC and to determine the distribution of pulmonary dysfunction in patients with UC.

Materials and Methods

A total of 39 cases of UC, were enrolled consecutively in this study from the Department of Gastroenterology, of a Medical College in North India, between June 2020 and October 2021. UC was diagnosed based on clinical
manifestations, colonoscopy, and pathological examination of the mucosa or intestinal tissues according to the World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD (2010) [12]. The extent and activity of UC were assessed endoscopically with Truelove and Witts score [13]. At the same time, 24 healthy subjects were collected as control from those who came to the hospital for a health examination. Chronic disease history of the intestinal tract and respiratory system were excluded, but there may be long-term chronic smoking history.

Exclusion criteria of UC patients were as follows: patients with a history of chronic respiratory disease, a history of smoking, exposure to harmful dust, and a history of upper respiratory tract infection within 1 month; pregnancy or breastfeeding; prior bowel resection leading to diarrhea, and/or pouch formation, toxic megacolon, hemorrhagic diathesis, present or past colorectal cancer; abnormal liver/kidney function tests.

Blood samples were collected for the measurements of hemoglobin, complete blood count (CBC), C-reaction protein (CRP), erythrocyte sedimentation rate (ESR) and liver function tests. This study was approved by the Ethics Committee of our hospital (No.: SHSY-IEC-pap-12-1), and signed informed consent was collected before the study.

The age, sex, family history, duration of disease, biochemical parameters (CBC, CRP, ESR, etc.), lung function test, chest X-ray, and duration of disease were collected. Patients and controls underwent standard pulmonary function testing. The vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in first second (FEV₁), and forced peak expiratory flow 25-75% (FEF25-75%) were recorded. The spirometry (Master Screen spirometer, Jaeger, Würzburg, Germany), and pulmonary function test was conducted by the same clinician. To avoid the impact of body surface on lung function, results were normalized by the predicted value (%). As we know, lung ventilation is the process of gas exchange between the lungs and the outside environment while lung diffusion is the process of gas exchange within the lungs. The measurements of VC, FVC, and FEV₁ are usually used to estimate ventilation function and FEF25-75% can reflect the severity of airway obstruction. In this study, either abnormality in ventilatory function, or diffuse function, or residual volume was defined as lung dysfunction.

For sputum induction, sputum was induced with 3%, 4% and 5% saline inhaled in sequence for 5 min via an ultrasonic nebulizer (Medix, Harlow, UK). After each inhalation patients expectorated into a sterile pot. Sputum free of salivary contamination was selected and was mixed with four times its volume of 0.1% dithiothreitol. From the induced sputum sample, a differential cell count was obtained from a cytospin preparation stained with Romanowski’s stain, and a total cell count was determined using a haemocytometer. Cell counting was performed by an experienced observer blind to the subject’s clinical characteristics.
Statistical analysis

PASW statistics (18.0, Polar Engineering and Consulting, Chicago, IL) was used for the statistical analysis. Comparisons of rates among multiple groups were done with Fisher exact test, continuous variables were compared with one-way ANOVA. The Chi-square test was used to find an association between independent and dependent variables. A value of $P$ less than .05 was considered statistically significant.

Results

The mean age of study for the control group was 35.8±3.8 years, whereas the mean age for subjects with active UC and inactive UC was 39.3±3.4 years and 40.9±7.1 years respectively. The male and female subjects in the active UC group were 70.0% and 30.0% respectively. According to the truelove index, the severity of active UC was moderate and severe among 36.7% and 63.3% of subjects respectively.

Table 1. Demographic and clinical profile of the study subjects (N=63)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number (%)/ Mean±SD</th>
<th>Controls (n=24)</th>
<th>Active UC (n=30)</th>
<th>Inactive UC (n=9)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td></td>
<td>35.8±3.8</td>
<td>39.3±3.4</td>
<td>40.9±7.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>15 (62.5)</td>
<td>9 (37.5)</td>
<td>24 (100.0)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>21 (70.0)</td>
<td>9 (30.0)</td>
<td>30 (100.0)</td>
<td></td>
</tr>
<tr>
<td>H/o smoking</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>9 (100.0)</td>
<td>=0.0001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24 (100.0)</td>
<td>30 (100.0)</td>
<td>0 (0.0)</td>
<td>=0.0001</td>
<td></td>
</tr>
<tr>
<td>Duration of disease (in months)</td>
<td></td>
<td>2.4±0.6</td>
<td>6.4±1.8</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Truelove Index</td>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0 (0.0)</td>
<td>9 (100.0)</td>
<td>11 (36.7)</td>
<td>19 (63.3)</td>
<td>=0.0001</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>19 (63.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.2±3.1</td>
<td>18.3±3.2</td>
<td>19.5±2.9</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Walking distance for 6-min walking test (in meters)</td>
<td>488.3±30.6</td>
<td>147.1±33.9</td>
<td>167.5±29.3</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

The pulmonary function test “FCV” showed reduced mean FCV among subjects with active UC (2.86±0.77 litres) and inactive UC (3.91±0.62 litres) as compared to
controls (4.04±1.14 litres). The percentage of mean FEV1 among subjects with active UC was 72.6%, 84.5% among inactive UC and 86.1% among controls. The ratio of FEV1/FCV was also reduced among active UC subjects (83.0%) and inactive UC subjects (84.2%) as compared to controls (86.1%). FEF25-75%, was also reduced among active UC subjects (59.5%) and inactive UC subjects (65.3%) as compared to controls (92.1%). Among the patients with deranged PFT, 1 (7.6%) had obstructive, 7 (53.8%) had small airway disease and 5 (38.6%) had a restrictive pattern of lung involvement.

Table 2. Pulmonary function tests among study subjects (N=63)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=24)</th>
<th>Active UC (n=30)</th>
<th>Inactive UC (n=9)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, litres (%)</td>
<td>4.04±1.14 (86.4)</td>
<td>2.86±0.77 (67.0)</td>
<td>3.91±0.62 (89.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV1, litres (%)</td>
<td>3.17±1.06 (86.1)</td>
<td>2.14±0.54 (72.6)</td>
<td>3.00±0.59 (84.5)</td>
<td>0.042</td>
</tr>
<tr>
<td>FEV1/FCV (%)</td>
<td>86.1</td>
<td>83.0</td>
<td>84.2</td>
<td></td>
</tr>
<tr>
<td>FEF25-75%, litres (%)</td>
<td>2.55±0.97 (92.1)</td>
<td>1.75±0.32 (59.5)</td>
<td>2.08±0.21 (65.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The blood pathological examination showed that the Eosinophil count was raised among active UC subjects (5.4±4.2 cell/HPF) and inactive UC subjects (3.3±0.3 cell/HPF) when compared with controls (0.5±0.2 cell/HPF). Also, Epithelial cell count was raised among active UC subjects (2.2±0.5 cell/HPF) and inactive UC subjects (2.5±0.8 cell/HPF) when compared with controls (0.6±0.3 cell/HPF). Differential cell count showed that the mean percentage of lymphocytes were raised in active UC (35.1%) and inactive UC (29.8%) as compared to controls (9.8%). Mean percentage of macrophages were reduced in active UC (24.1%) and inactive UC (32.2%) as compared to controls (70.3%).

Table 3. Absolute cell count and differential cell count in induced sputum among study subjects (N=63)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n=24)</th>
<th>Active UC (n=30)</th>
<th>Inactive UC (n=9)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>7.5±1.6 (18.7)</td>
<td>7.3±1.1 (19.7)</td>
<td>6.2±0.5 (15.1)</td>
<td>0.034</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.5±0.2 (0.08)</td>
<td>5.4±4.2 (14.8)</td>
<td>3.3±0.3 (13.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>4.7±2.2 (9.8)</td>
<td>14.6±5.6 (35.1)</td>
<td>8.1±4.6 (29.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Macrophages</td>
<td>30.2±2.8 (70.3)</td>
<td>11.6±2.7 (24.1)</td>
<td>11.4±0.9 (32.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Epithelial cell</td>
<td>0.6±0.3 (0.2)</td>
<td>2.2±0.5 (5.5)</td>
<td>2.5±0.8 (9.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Discussion**

Patients with UC are known to have several extraintestinal manifestations including pulmonary involvement. Douglas et al., found PFT abnormalities in 32% of patients with UC [14]. However, most of the patients in their study were
smokers. In our study, all participants were non-smokers or ex-smokers (9 out of 63) and thus any possible negative impact of smoking on PFT results was negligible. Sethy et al., and Tzanakis et al., also found deranged PFT in 17% (n = 85) and 27% (n = 51) patients with UC [15,16].

We found that UC patients had significantly lower FCV as compared with controls. The reduction in FCV may indicate an involvement of the lung parenchyma. This observation indicates that subclinical interstitial lung disease may be present in patients with UC as it is known that a reduction in the FCV of the lungs is a common and early manifestation of interstitial lung disease [17]. The observed reduction in FCV in our study might well be consistent with the presence of a subclinical alveolitis supporting the hypothesis of the migration of an inflammation via the bloodstream, from the intestine into both lung parenchyma and airway mucosa [18]. Small airway function (decreased FEF25-75%) was significantly impaired in patients with UC as compared with controls in our study. Tzanakis et al., found alteration in the function of small airways independent of the presence of atopy in patients with UC even without pulmonary symptoms [19].

Mild airway inflammation, secondary to the primary inflammation of the intestinal mucosa, could explain the alteration in the small airways seen in our study. Changes in the bronchial epithelium, consisting of basal cell hyperplasia, basement membrane thickening, submucosal inflammation, and an overall increase in thickness of the epithelium, have been reported in bronchial biopsies from patients with UC and coexisting bronchial suppuration [11].

All UC patients, whether active or inactive, had abnormal PFT as compared with healthy controls in our study. Thus, it may suggest that patients, even after remission of UC, may continue to have deranged PFT. Also, in our study, FCV, FEV1, FEV1/FVC ratio, and FEF25-75% were significantly decreased in patients with active or inactive disease as compared with controls. Patients with active disease had lower FCV, FEV1, FEV1/FVC ratio, and FEF25-75% than in inactive disease, and it was statistically significant. Herrlinger et al., and Mohamed-Hussein et al., also found that FEV1 and FVC significantly decreased in patients with active disease as compared to those with an inactive disease [7,20]. In another study, Fehmi et al., found significantly decreased FEV1, FVC, and DLCO when PFT in the active and in remission phases in the same patient was compared with control [21].

Among the patients with deranged PFT, 1 (7.6%) had obstructive, 7 (53.8%) had small airway disease and 5 (38.6%) had a restrictive pattern of lung involvement. Sethy et al., reported restrictive pattern and small airway disease in 16% and 8% of UC patients (n = 51) with abnormal PFT [22]. Godet et al., also found PFT abnormalities, obstructive pattern, abnormal DLCO, and restrictive pattern in 53%, 22.7%, 28.8%, and 1.5%, of patients with UC, respectively [23]. In an Indian study of 27 of 95 (28.5%) patients with inflammatory bowel disease (83 UC and 12 Crohn’s disease), small airway obstruction was seen in 18, restrictive defect in 6, and mixed defect in 3 patients [24]. Our results are somewhat in accordance with that study.
Patients with severe disease activity may perform worse on PFT due to general sickness and fatigue. Apart from poor compliance in performing the tests being an exclusion criterion in our study, patients in remission without clinical symptoms performed significantly worse than healthy controls. This is a strong argument on the influence of the disease on pulmonary function and strengthens the hypothesis that the observed abnormalities in lung function tests represent a real extraintestinal manifestation of UC. Limitation of our study is lack of high-resolution CT scan of thorax in patients with abnormal PFT, which may have further characterized the respiratory abnormality. Also, long-term follow-up of patients with abnormal PFT is required to know whether they develop clinically significant lung disease or end stage lung failure.

**Conclusion**

In summary, taken together, subclinical pulmonary dysfunction is frequent in UC and dependent on disease activity. Some alterations were sub-clinical and some of the patient showed troublesome pulmonary symptoms. Pathophysiological mechanisms and clinical relevance are to be further clarified. Early detection is important as both the alveolar and airway disease often respond well to steroid treatment.

**References**