Respiratory Medicine (2007) **101**, 977–982

ELSEVIER

respiratoryMEDICINE

# Changes in pulmonary function in patients with ulcerative colitis

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Received 11 April 2006; accepted 5 September 2006
Available online 17 October 2006

**KEYWORDS**
Ulcerative colitis;
Pulmonary functions;
Sputum lymphocytosis

**Summary**
*Objectives:* Information on the occurrence and frequency of pulmonary involvement in patients with ulcerative colitis (UC) is inconsistent. Some authors reported pulmonary impairment with UC by standard pulmonary function tests (PFTs) and documented a reduced diffusing capacity for carbon monoxide (DLCO) especially in patients with active disease, whereas others could not detect differences in routine PFTs between UC patients and controls.
*Aim:* The aim of this prospective study was to determine the frequency and type of pulmonary dysfunction in patients with UC with respect to disease activity. Furthermore, to evaluate the influence of smoking, nutritional status, sputum cytology and sulphasalazine therapy on PFT parameters.
*Patients and methods:* Twenty-six patients with UC (20 with active disease, 6 inactive) and 16 age and sex matched healthy controls were investigated with respect to the following pulmonary function tests, forced vital capacity (FVC), forced expiratory volume in the 1 s ($FEV_1$%) and their ratio ($FEV_1$/FVC) and forced expiratory flow 25–75% (FEF25–75%) as well as oxygen saturation. For UC patients, colonoscopy and biopsy were done. Disease activity was assessed by Truelove index for UC. Induced sputum was sampled for cytology. Smoking habit, body mass index (BMI) and medications were recorded.
*Results:* Fifteen out of 26 patients with UC (57.6%) exhibited at least one pathological pulmonary function test (<80% of predicted value). Small airway obstruction was reported in the 15 patients, restrictive dysfunction in 30.7% and obstructive dysfunction in 11.5%. The impairment of PFTs was significant and more pronounced in patients with active disease, FVC (−14% of predicted), $FEV_1$ (−9% of predicted) and FEF25–75% (−32% of predicted), $P<0.01$, 0.05 and 0.01, respectively. There was no significant influence of smoking and medications on PFTs.

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0954-6111/$ - see front matter 
doi:10.1016/j.rmed.2006.09.005

*Conclusions:* UC patients show significantly decreased lung function tests in comparison to healthy controls. The impairment in active disease exceeded that during the remission. Early recognition is important, as they can be strikingly steroid responsive.


## Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are associated with a variety of systemic manifestations involving the respiratory system. Many authors have previously shown that subjects with unexplained cough[1–3] and non-smoking subjects with fixed airflow obstruction[4] have a high prevalence of organ-specific autoimmune disease and a high prevalence of organ-specific auto antibodies. Subjects with inflammatory bowel disease report common respiratory symptoms more often than healthy controls.[5] They have suggested that the increased respiratory symptoms are due to airway inflammation as a result of aberrant homing of inflammatory cells to the lungs from the primary site of chronic inflammation.[1,2,4]

The presence of sub clinical disease in patients with minimal respiratory symptoms was suggested and the pulmonary function abnormalities have revealed inconsistent results. Whereas some authors could not detect differences in routine pulmonary function test between IBD patients and controls,[3,6,7] others, documented changes including a decrease in gas transfer factor,[8,9] an elevated functional residual capacity (FRC) and raised residual volume (RV) during periods of active bowel disease,[10,11] decrease in maximal mid expiratory flow rate[12] and an increased frequency of bronchial hyperresponsiveness.[12] Furthermore, alveolar lymphocytosis was evident in bronchoalveolar lavage fluid from CD patients without respiratory symptoms.[13]

The pulmonary impairment in IBD patients may be related to disease activity.[14,15] Also, side effects of treatments may contribute to pulmonary dysfunction in IBD patients.[16] Hypersensitivity pneumonitis is rare, but has been reported in some cases for sulfasalazine and mesalazine.[17,18]

*The aim of this prospective study* was to determine the frequency and type of pulmonary dysfunction in patients with UC with respect to disease activity. Furthermore, the implication of smoking, nutritional status, sputum cytology and sulphasalazine therapy on pulmonary function will be discussed.

## Subjects and methods

The study was conducted in Tropical Medicine and Gastroenterology Departments and Chest Department, Assiut University Hospital, Egypt. Twenty-six patients with UC were enrolled in this prospective study. Age and sex matched normal controls (16 subjects) were recruited from healthy volunteers living in the same neighborhood.

Patients with UC were diagnosed by thorough history, full clinical examination. Pulmonary symptoms and signs were recorded in their entry sheets. Laboratory investigations including complete blood count (CBC), erythrocyte sedimentation rate (ESR) and liver function tests were done. Abdominal ultra-sonography, colonoscopy and colonic biopsy and plain X-ray chest were performed. Smoking habits and medications were documented in every patient.

### UC disease activity

The activity of ulcerative colitis was assessed using the Truelove score.[19] This score include stool frequency, fever, the occurrence of blood in stool and, laboratory findings, as hemoglobin levels (HB) and erythrocyte sedimentation rate (ESR). Patients with Truelove indices of mild were considered to be in remission and patients with indices moderate and severe had active disease.

### Pulmonary function tests, $O_2$ saturation and 6-min walking test

Pulmonary function testing were performed utilizing Sensor Medics Corporation Spirometer (Model CA92687, SN 54065, Osaka, Japan), to measure the predicted forced vital capacity (FVC%), the predicted forced expiratory volume in the 1 s ($FEV_1$%) and their ratio ($FEV_1$/FVC) as well as forced expiratory flow 25–75% (FEF25–75%). Each measurement was repeated at least three times and the highest acceptable measurement was compared with normal predicted value. Oxygen saturation was measured using radiometer acid–base analyzer ABL 30. Unfortunately, the diffusing capacity for carbon monoxide (DLCO) was not measured as it is not available in our center. Walking distance after 6 min walking test was calculated to indicate the presence and degree of dyspnea in patients and controls.

### Sputum cytology

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.

### Exclusion criteria

Reasons for exclusion from this study were abnormal X- ray chest, signs of infectious bronchitis or pneumonia, and lack

of compliance in performing lung function tests. Also, patients with history of associated chronic diseases (cardiac, renal, hepatic disease, diabetes or hypertension), methotrexate or steroid therapy were excluded.

### Statistical analysis

All statistical analyses were performed using the statistical package SPSS 10.0 for windows (SPSS, Chicago, IL). Data were tested for normal distribution, expressed as mean $\pm$SD. Analysis of variance by Mann–Whitney test was used to compare means, and Spearman's $\rho$ correlation was used after simple regression to calculate correlation coefficients. $P$ values $<0.05$ were considered to be statistically significant.

### Ethical considerations

Informed consent was obtained from all patients and control subjects, and the study was approved by the ethical committee of the Faculty of Medicine, Assiut University Hospital, Egypt.

## Results

Twenty-six patients, 17 males and 9 females (65%/35%) as well as 16 healthy controls, with mean age $39.5\pm4$ and $34.7\pm3$ years old, respectively, were recruited in the study. The demographic and clinical data of the studied individuals are summarized in Table 1.

### Frequency of respiratory symptoms

Dyspnea on excursion (breathlessness) was the commonest presenting symptom in patients with all patterns of disease (40% in patients with active UC, 35% in patients with inactive UC vs. none of controls, $P<0.001$ in both). Dry cough was recorded in 25% of patients with active UC and in 15% of patients with inactive disease ($P<0.01$ and 0.05 vs. controls). Sputum production was recorded in 20% of patients with active UC, but none of patients with inactive disease had sputum ($P<0.01$ vs. inactive UC and controls). None of the patients had history of chest wheeze, heamoptysis or chest pain. The walking distance was significantly lower in patients with active disease vs. inactive cases and controls ($145.9\pm32.8$ vs. $166.4\pm28.2$ and $487.2\pm29.5$ m, respectively ($P<0.01$ and 0.000). However, no significant difference in $O_2$ saturation was recorded in active UC ($95\pm97.8\%$), inactive UC ($94.8\pm98.1\%$) compared to controls ($97.2\pm98.7\%$).

### Pulmonary function tests in UC patients versus controls

Fifteen out of 26 patients (57.6%) exhibited at least one pathological pulmonary function test ($<$ 80% of predicted value). Small airway obstruction (as evidenced by diminished FEF 25–75%) was reported in the 15 patients (57.6%), restrictive dysfunction in 8 patients (30.7%) and obstructive dysfunction in 3 patients (11.5%). The mean values of FVC, $FEV_1$, $FEV_1$/FVC% and FEF25–75% as well as the percentage of predicted normal were recorded in patients and controls in Table 2.

The impairment in PFTs was significant and more pronounced in patients with active UC versus controls, FVC ($-14\%$ of predicted), $FEV_1$ ($-8.5\%$ of predicted), and FEF25–75% ($-32\%$ of predicted), $P<0.01$, 0.05 and 0.01, respectively. Also, the changes in pulmonary functions were significantly evident in patients with active UC vs. patients with inactive UC (Table 2).

### Sputum cytology results

In Table 3, induced sputum cytology results demonstrated significant increase in absolute and differential lymphocytic

**Table 1** Demographic and clinical data of the studied groups.

| Variable | Active UC ($n=20$) | Inactive UC (6) | Controls ($n=16$) | $P$-value |
|---|---|---|---|---|
| Male/female | 14/6 | 3/3 | 10/6 | NS |
| Smokers | 0 | 3 | 0 | NS |
| Age, years (mean$\pm$SD) range | $38.2\pm3$<br>16–45 | $39.8\pm7$<br>16–45 | $34.7\pm3$<br>22–38 | NS |
| Treatment | 0 | 6 | 0 | — |
| Duration of the disease, months (mean$\pm$SD) (range) | 2.3+0.5<br>1–3 | $6.3\pm1.7$<br>1–36 | 0 | — |
| Truelove index | Moderate, severe | Mild | 0 | — |
| BMI (kg/m$^2$) (mean$\pm$SD)<br>Range | $17.2\pm3$*<br>15.2–23.3 | 18.4+2.8<br>16.2–20.4 | $23.1\pm3$<br>18–26.1 | 0.001* |
| Walking distance, meters (6 MWT) | $145.9\pm32.8$* | $166.4\pm28.2$† | $487.2\pm29.5$ | 0.000*<br>0.01† |

BMI = body mass index, 6 MWT = 6-min walking test, UC = ulcerative colitis.

*Comparison between active ulcerative colitis patients and controls.

†Comparison between active ulcerative colitis patients and inactive UC patients. Mann–Whitney test was used to compare the non-parametric means.

**Table 2** Changes in pulmonary function parameters in patients with active, inactive UC and controls (mean ± SD).

| Variable | Active UC (20) | Inactive UC (6) | Controls (16) |
|---|---|---|---|
| FVC, liters (%) | 2.75 ± 0.66* (66) | 3.80 ± 0.51(88.7)† | 3.93 ± 1.03 (85.3) |
| $FEV_1$, liters (%) | 2.03 ± 0.43* (71.5) | 2.99 ± 0.48 (83.4)$ | 3.06 ± 0.95 (85.0) |
| $FEV_1$/FVC% | 82.9 | 83.1 | 85.0 |
| FEF25–75%, Liters/s (%) | 1.64 ± 0.21* (58.4) | 1.97 ± 0.19‡ (64.2)$ | 2.44 ± 0.86 (91)$ |

Data are expressed as mean +SD and percentage of predicted (%), $P<0.05$ was considered significant (Mann–Whitney test).
*Comparison between active UC and controls.
†Comparison between active UC and inactive.
‡Comparison between inactive UC and controls.

**Table 3** Induced sputum cell counts and differential counts in the studied groups.

| Variable | Active UC (20 patients) | Inactive UC (6 patients) | Controls (16 subjects) |
|---|---|---|---|
| Absolute cell count (cell/HPF) | | | |
| Neutrophils | 7.2 ± 0.9 | 6.1 ± 0.4 | 7.4 ± 1.5 |
| Eosinophils | 5.3 ± 4.1* | 3.2 ± 0.2†,‡ | 0.4 ± 0.1 |
| Lymphocytes | 13.5 ± 5.3* | 8.0 ± 4.5†,‡ | 4.6 ± 2.1 |
| Macrophages | 10.5 ± 2.6* | 10.3 ± 0.8† | 29.1 ± 2.7 |
| Epithelial cell | 2.1 ± 0.4 | 2.4 ± 0.7 | 0.5 ± 0.2 |
| Differential cell counts (%) | | | |
| Neutrophils | 18.6 | 14.1 | 17.6 |
| Eosinophils | 13.7* | 12.3† | 0.09 |
| Lymphocytes | 34.9* | 30.7† | 10.9 |
| Macrophages | 27.2* | 39.6†,‡ | 69.4 |
| Epithelial cell | 5.4* | 9.2†,‡ | 0.1 |

HPF = high power field, data were expressed as mean ± SD or %.
* # $ = $P< 0.05$ (Mann–Whitney test).
*Comparison between active UC and controls.
†Comparison between inactive UC and controls.
‡Comparison between active UC and inactive.

and eosinophilic counts compared to controls ($P< 0.01$ and 0.05). The induced sputum lymphocytosis and eosinophilia were more pronounced in active UC compared to inactive UC.

### Correlation between pulmonary function parameters with disease activity, BMI, smoking, treatment, and sputum lymphocytosis and eosinophilia

We noticed significant negative correlation between UC activity, sputum lymphocytosis, eosinophilia and pulmonary function parameters (FVC%, $FEV_1$% and FEF25–75%). Also, there was significant positive correlation between BMI and PFT parameters. No, correlation between sulphasalazine therapy and PFTs parameters or between sulphasalazine and induced sputum lymphocytosis. The number of smokers in this study was a limitation factor in doing proper correlation (smokers were only 3 subjects). So, it was unlikely that smoking contributed to the pulmonary disease in the studied group (Table 4).

## Discussion

UC is a chronic idiopathic inflammatory bowel disease with remissions and exacerbations. The prevalence of UC in Egypt is increasing, and in one study the frequency of new cases of UC was 25 cases in year 1997 increased to 52 cases in year 1999.[20]

The true prevalence of the association between lung disease and IBD remains unknown, and although it was only found in three of 1400 cases in one study,[21] various factors suggest that this figure is an underestimate of the true prevalence of the association. Firstly, clinicians may not consider this association as patients often present with pulmonary symptoms years after the bowel disease change and after being discharged from gastrointestinal follow-up.[4] Asymptomatic patients can have abnormal pulmonary function[8,12] or alveolar lymphocytosis[13] and therefore may not present to a respiratory physician.

We investigated the frequency and type of abnormal pulmonary function in patients with ulcerative colitis in comparison with normal age and sex-matched healthy controls. Also, the influences of disease activity, sulphasalazine

**Table 4** Correlation between pulmonary function parameters with disease activity, BMI, treatment, and sputum lymphocytosis and sputum eosinophilia.

| | FVC% | $FEV_1$% | Ratio | FEF25–75% | Sputum lymphocytosis |
|---|---|---|---|---|---|
| Disease activity | $r = -0.327$* | $r = -0.470$‡ | NS | $r$ = -0.670‡ | $r = 0.552$‡ |
| BMI | $r = 0.255$* | $r = 0.343$‡ | NS | $r = 0.430$‡ | — |
| Sulphasalazine therapy | NS | NS | NS | NS | NS |
| Sputum lymphocytosis | $r = -0.330$‡ | r = - 0.361‡ | NS | $r = -0.441$‡ | — |
| Sputum eosinophilia | $r = -0.462$‡ | $r = -0.287$* | NS | $r = -0.694$‡ | $r = 0.459$‡ |

Spearman's $\rho$ correlation for non-parametric variables.
*Correlation is significant at the $<0.05$ level (2-tailed).
‡Correlation is significant at the $<0.01$ level (2-tailed).

medication, smoking, sputum cytology and body mass index were analyzed.

In this study, patients with active UC had respiratory symptoms in the form of dyspnea on exersion (40% vs. 33.3% in patients with active vs. inactive UC). Dry cough was recorded in 20%, 16% of patients with active and inactive UC. These results are similar to the findings of Birring et al., who recorded dyspnea and cough in 36% and 24% of patients with treated UC and Crohn' disease.[3] Also, in the present study it was found that the sputum production was recorded in 20% of patients with active UC and none of the patients with inactive disease. Similarly, copious sputum production was reported as a characteristic feature of the bronchiectasis associated with UC in some studies.[12,22]

We detected abnormal results in pulmonary function tests (defined as $<80$% of predicted value) in a surprisingly large proportion of UC patients (57.6%). The most common abnormality was the decrease in FEF25–75%. Similar results of decrease in maximal mid expiratory flow rate were found in about 22% of cases with UC.[11,23] Furthermore, we recorded significant reduction of FVC, $FEV_1$ in patients with active UC compared to inactive group and controls, while the ratio of $FEV_1$/FVC% was not significantly different. These results are consistent with earlier results suggesting a restrictive pattern of lung function impairment in UC patients (this was recorded in 30.7% of our cases).[7,11,15] The diffusing capacity of carbon monoxide (DLCO) seems to be a very important limitation in our study. Earlier studies measuring DLCO in inflammatory bowel diseases, did not find an influence of the disease,[13,23] but recent studies found DLCO to be significantly diminished specially in active disease.[14,15] Early endothelial involvement is common inflammatory bowel disease and may affect lung endothelial as well.[24]

The influence of disease activity was studied. We found that the mean values as well as the percentage of predicted FVC, $FEV_1$, FEF25–75% were significantly lower in patients with active UC vs. inactive disease and with significant negative correlation between these indices of PFTs and disease activity. Herrlinger et al. recorded similar results in 45% of UC patients with active disease and added that alterations in PFTs are more frequent in active cases and persist during remission.[15]

It is important to consider whether therapy with sulphasalazine or mesalazine may have been responsible for the pulmonary changes. The most common abnormality described in association with sulphasalazine therapy is upper lobe peripheral opacities, although lower lobe opacities, eosinophilic pneumonia, interstitial pneumonitis, BOOP and cavitating nodules have also been reported.[16–18] Six of our patients were taking sulfasalazine for more than 6 months. There was no radiologic evidence of similar involvements. Furthermore, none of these patients had peripheral blood eosinophilia, which is usually present in lung disease caused by sulphasalazine. Moreover, there was no correlation between sulphasalazine use and the changes recorded neither in PFTs indices nor with sputum lymphocytosis. These features make it unlikely that the drug contributed to the pulmonary abnormalities seen in the patients. However, we noticed induced sputum eosinophilia (absolute and differential) in this group which may be an early indication that longer duration of this group of drugs may affect the lung; therefore, monitoring the side effect of this drug should be done on larger scale of patients to further clarify this point.

The nutritional status has been shown to have significant influence on the overall pulmonary function in patients with inflammatory bowel disease. Christie and Hill demonstrated a 35% loss of body protein stores and associated –40% physiological impairment ($FEV_1$, FVC and maximal voluntary ventilation, MVV) in patients with acute exacerbations of CD compared to controls. There was significant immediate and delayed improvement of these parameters after 2 weeks of nutritional supplementation and further improvement on restoration of body proteins during convalescence.[25] Similarly, we examined the body mass index (BMI, $kg/m^2$) as an index of the nutritional status of both groups with UC and controls and we found significant positive correlation between BMI and pulmonary function results.

Lastly, the mechanism of pulmonary involvement in autoimmune diseases is unclear. One proposed mechanism for explaining this association is the common embryological derivation of the lungs and gastrointestinal tract from the primitive foregut, and the similarity in the immune systems in the pulmonary and intestinal mucosa.[4] Other theory suggested that lymphocytes sensitized from the GIT may induce inflammation on the mucosal surfaces of other organs. In CD, alveolar lymphocytosis has been reported among patients free of clinical symptoms.[13,26] A recent study investigating induced sputum in CD patients found the CD4/CD8 quotient to be abnormally high in patients with active disease relative to patients in remission.[27]

In support to this hypothesis, sputum lymphocytosis was recorded in all UC patients with pulmonary dysfunction in the present work, and the induced sputum lymphocytosis was significantly correlated with decrease in FVC, $FEV_1$ and FEF25–75%.

A large proportion of the patients had pulmonary disease that was responsive to steroids either orally as in the case of alveolar disease or inhaled or orally or both, in airway disease. These observations suggest that the pulmonary disease in CD and UC has an inflammatory basis.

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.

## Acknowledgments

I wish to express my profound gratitude to Professor Tarek Mahfouz Abdel-Meguid for his continuous criticism, guidance and encouragement through this work and other works. Also, many thanks to Dr. Mahmoud Risk, Lecturer of Pathology, Faculty of Medicine, Assiut University for his assistance in the cytological work-up of the sputum.

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