

ORIGINAL ARTICLE

Pulmonary function in patients with ulcerative colitis and its relationship with disease severity

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Abstract

Background and Aim: Ulcerative colitis (UC) patients have several extraintestinal and systemic manifestations. As studies on the frequency and predictors of pulmonary involvement in patients with UC are inconsistent, we undertook this prospective study.

Methods: Eighty-seven patients with UC (in remission 49, 56.3%, active disease 38, 43.6%, median age: 40 years, range: 16–66, 55, 62.2% males) and 50 healthy controls (median age: 38 years, range: 14–69, 34, 68% males) underwent pulmonary function tests (PFTs) including forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), Tiffeneau value (FEV₁/FVC), mid-expiratory flow rate, and diffusion lung capacity for carbon monoxide with spirometer.

Results: Subjects with UC and control were comparable in age and gender. PFT was abnormal in 24 (27.5%) patients (active disease 15/38, 39.4%, remission 9/49, 18.4%) and 1 (2%) control ($P < 0.005$). Of the 24 patients with abnormal PFT, small airway, restrictive, and obstructive defects were detected in 12 (50%), 11 (45.8%), and 1 (4.2%) patients, respectively. Patients with abnormal PFT more often had active disease (15/24, 62.5% vs 23/63, 36.5%; $P = 0.03$). No relation of PFT abnormalities was found with age, sex, duration of disease, body mass index, serum albumin, and hemoglobin levels, and other extraintestinal manifestation (arthritis/arthralgia) and drugs used to treat UC.

Conclusion: UC patients with active disease have abnormal pulmonary functions with predominant involvement of small airways. Active UC was more often associated with abnormal PFT than the disease in remission.

Introduction

Lung involvement in ulcerative colitis (UC), first reported in 1976,¹ has been increasingly reported in recent years. Since its first report, abnormal pulmonary function tests (PFTs) have been reported in 17–55% patients with UC,^{2–6} including a decrease in gas transfer factor (diffusion lung capacity for carbon monoxide [DLCO]),^{7,8} elevated functional residual capacity (FRC),⁹ decrease in maximal mid-expiratory flow rate (MEFR),¹⁰ or an increased frequency of bronchial hyperresponsiveness¹¹; however, in some studies, no abnormalities in PFT were found.^{10,12} Various respiratory abnormalities reported in patients with UC include obstructive and interstitial lung disease,¹³ small and large airway disorders,^{14,15} increase in bronchial sensitivity,¹¹ bronchitis, bronchiectasis,^{16,17} and bronchiolitis obliterans.¹⁸ Thus, it is important that respiratory manifestations are recognized and treated early. Otherwise, these may lead to irreversible changes in the airway wall or the end-stage lung disease.

However, information about the types of respiratory dysfunction, their relation with disease activity, and factors influencing pulmonary dysfunction in patients with UC is insufficient

and inconsistent. Also, little data are available from India regarding pulmonary function abnormalities in patients with UC.^{19–21}

Accordingly, we undertook a study with the following aims: (i) to evaluate the frequency and type of pulmonary dysfunction in patients with UC and (ii) to evaluate the predictors of abnormal pulmonary functions.

Methods

Patients. Eighty-seven patients with UC (diagnosis based on characteristic clinical features, colonoscopy and histopathological examination of colonic mucosa, and exclusion of infective cause) attending the Gastroenterology outpatient of a multilevel teaching hospital in northern India were subjected to PFT after obtaining informed consent. Detailed clinical history including demographic profile, duration, disease severity, activity, and clinical course was recorded.

Patients with major surgical operation and skeletal abnormalities in the thorax, history of asthma or familial atopy, peripheral eosinophilia, previous lung disease, active smoking,

chronic obstructive pulmonary disease (COPD), signs of pulmonary infection, end-stage renal disease (ESRD), coronary artery and valvular heart diseases, morbid obesity (body mass index [BMI] > 35 kg/m²), pregnancy, age < 14 or >70 years, use of non-steroidal anti-inflammatory drugs, and lack of compliance in performing PFT were excluded from the study.

Duration of disease. The duration of the disease was defined as the period between the date of onset of symptoms and the date of PFT.

Disease activity. Patients were divided into two groups depending on the activity of UC, one with active disease and the other in remission. Patients with active disease were classified as mild, moderate, or severe as per Truelove score.²² This score includes stool frequency, occurrence of blood in stools, fever, hemoglobin (Hb) levels, and erythrocyte sedimentation rate (ESR). Patients were considered in clinical remission if they had one or two stools a day without blood, no fever, or tachycardia, along with normal Hb determinations and ESRs.²³

Extent of disease. Extent of the disease was assessed on colonoscopy as proctitis, left-sided colitis, or pancolitis. Proctitis was defined as involvement of the rectum only, left-sided colitis as left colon up to splenic flexure and pancolitis as extensive disease beyond splenic flexure.

Healthy controls. A group of age- and sex-matched healthy controls was taken from the general population. PFT was done in all of them.

Ethical considerations. Written and informed consent was taken from all the patients and controls. The study protocol was approved by the ethics committee of the institution.

Pulmonary function test. Pulmonary function testing were performed with spirometer (2010 Ganshorn, Medizin Electronic GmbH Industries, Trasse 6-8, 97618, Nieder Lauer, Germany. Software version LF 8.5) to measure the predicted forced vital capacity (FVC), the predicted forced expiratory volume in 1 s (FEV₁), and their ratio (FEV₁/FVC) as well as mean expiratory volume 25–75 (MEV_{25–75}). A minimum of three acceptable and reproducible maneuvers were obtained, according to standard recommended by American Thoracic Society. Results were expressed as percentage of normal for gender, age, and height (percent predicted). DLCO was measured by single breath test²⁴ (2010 Ganshorn, Medizin Electronic GmbH Industries, Trasse 6-8, 97618. Software version LF 8).

The individual results were classified as normal, restrictive, obstructive, or small airway disease as per the American Thoracic Society guidelines for PFT.²⁵ Normal physiology was defined by all measurements being >80% predicted, a restrictive defect as a reduced (<80% predicted) FVC with an FEV₁/FVC ratio of >70% predicted or reduced DLCO (<80% predicted), and an obstructive defect as a reduced FEV₁ with a normal FVC and a low FEV₁/FVC ratio (<70% predicted). Small airway disease was defined as reduced FEV₁ (<70% predicted), low FEV₁/FVC (<70% predicted) ratio, and reduced MEF_{25–75} (<60% predicted).

Statistical analysis

Sample size calculation. Assuming frequency of abnormal PFT among subjects with UC and healthy controls to be 20% and 4%, respectively, sample size was calculated considering 1.5 cases for every control with two-sided confidence interval of 95% and power of 80% with *P*-value of <0.05 as significant; number of cases and controls needed were 72 and 48, respectively. For calculation of sample size, EpiInfo software version 7 - (Center for Disease Control and Prevention, Atlanta, GA, USA) was used.

Data analysis. Statistical analysis was performed using SPSS version 15 (SPSS, Inc., Chicago, IL, USA). Continuous data were expressed as median and range. Continuous and categorical variables were analyzed using Mann–Whitney *U*-test and chi-square test with Yates' correction as applicable, respectively. Intergroup comparison of more than two variables was performed using Kruskal–Wallis *H*-test. Spearman or Pearson correlation coefficient was used to find out the relationship between the two continuous variables depending on distribution of the data. *P*-values <0.05 were considered significant.

Results

Demographic and clinical characteristics of UC patients and controls.

Table 1 summarizes demographic, clinical, and laboratory parameters of patients with UC (*n* = 87) and control (*n* = 50). Patients with UC and healthy controls were comparable in age (median: 40 years, range: 16–66 and median: 38 years, range: 14–69; *P* = 0.7) and gender (male 55, 63.2% and 34, 68%; *P* = 0.5). Duration of disease was 48 (range: 1–240) months. Forty-nine (58.6%) patients had active disease, 12 (arthralgia in 3 and arthritis in 9) had peripheral arthritis/arthralgia as extraintestinal manifestation of UC. Three patients were ex-smokers and the others were non-smokers. All controls were non-smokers. None of our patients had an occupational or family history of respiratory disease, atopy, or had major abdominal or thoracic surgery. No patient had any significant abnormality on chest radiograph.

PFT in UC patients. Twenty-four (27.6%) UC patients but only 1 (2%) control showed abnormal PFT (*P* < 0.01). Of the 24 patients with abnormal PFT, small airway, restrictive, and obstructive defects were detected in 12 (50%), 11 (45.8%), and 1 (4.2%) patients, respectively. UC patients had significantly low FEV₁, FEV₁/FVC, MEF_{25–75}, peak expiratory flow rate (PEFR), and DLCO values compared with controls (*P* < 0.05) as shown in Table 1. PFT values were abnormal in 3 of 24 (12.5%), 15 of 42 (35.7), and 6 of 21 (28.6%) patients with proctitis, left-sided colitis, and pancolitis, respectively, as shown in Table 2. Of the 24 patients with abnormal PFT, 5 had symptoms (chronic cough in 3 and dyspnoea on exertion in 2).

Relationship between disease activity, extent of colitis, extraintestinal manifestations, treatment and nutrition status, and PFT.

The demographic, clinical, and laboratory parameters of UC patients with normal and abnormal PFT are shown in Table 2. In patients with abnormal PFT, 15 (62.5%) had active disease while 9 (37.5%) were in

Table 1 Demographic, clinical, laboratory parameters, and PFT of patients and controls

Parameters	Patients (<i>n</i> = 87)	Healthy controls (<i>n</i> = 50)	<i>P</i> -value
Age (years), median (range)	40 (16–66)	38 (14–69)	0.70
Sex (males), <i>n</i> (%)	55 (63.2)	34 (68)	0.57
Mean duration of disease (months)	48 (1–240)		
Drugs			
ASA (%)	78 (89.7)		
Steroids (%)	39 (44.8)		
Azathioprine (%)	16 (18.4)		
Methotrexate (%)	2 (2.3)		
Sulfasalazine (%)	9 (10.3)		
Extent of disease			
Proctitis (%)	24 (27.6)		
Left-sided colitis (%)	42 (48.3)		
Pancolitis (%)	21 (24.1)		
Disease activity			
Remission (%)	49 (56.6)		
Relapse (%)	38 (43.4)		
Mild (%)	6 (15.8)		
Moderate (%)	9 (23.7)		
Severe (%)	23 (60.5)		
Hemoglobin (g/dL)	11.8 (5.3–17.2)		
Albumin (g/dL)	3.9 (1.6–4.9)		
BMI (kg/m ²), median (range)	20.9 (14.8–34.2)	23.1 (15.9–34.9)	0.83
Abnormal PFT, <i>n</i> (%)	24 (27.6)	1 (2)	<0.01
FEV ₁ median (range)	89(51–171)	98 (71–181)	0.000
FEV ₁ /FVC median (range)	86 (63–120)	91 (80–118)	0.048
FVC median (range)	87 (49–145)	92.5 (80–145)	0.005
MEF _{25–75} median (range)	77 (24–176)	91.5 (67–176)	0.000
PEFR median (range)	79(38–122)	96.5 (70–140)	0.000
DLCO median (range)	108 (68–213)	122 (82–213)	0.000

Mann–Whitney *U*-test for continuous data and chi-square test for categorical data. All continuous data are presented as median and range. For categorical data, figures within parenthesis indicate percentages.

ASA, amino salicylic acid; BMI, body mass index; DLCO, diffusion lung capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mean expiratory flow, PEFR, peak expiratory flow rate; PFT, pulmonary function test.

remission ($P < 0.03$). Patients with proctitis tended more often to have normal than abnormal PFT (12.5% vs 33.3%; $n = 0.06$; Table 2). Nutritional status (BMI, serum albumin, and Hb) was not significantly different in patients with normal and abnormal PFT. Of the 87 patients with UC, 12 (13.8%) had peripheral joint arthralgia/arthritis. Frequency of abnormal PFT was comparable among patients with or without arthralgia/arthritis (4/24, 16.6% vs 8/55, 14.5%; $P = ns$). There was no relationship between treatment of UC with different drugs and abnormal PFT (Table 2).

UC patients with active disease and remission.

Patients with active disease were comparable in age, gender, and duration of disease with patients in remission. There was no significant difference in FEV₁, FEV₁/FVC, MEF_{25–75}, PEFR, and DLCO ($P > 0.05$) among patients with UC with active disease or in remission (Table 3), although different from controls (Fig. 1).

Discussion

In the present study, we found that (i) patients with UC more often had abnormal PFT in comparison to healthy controls,

(ii) patients with abnormal PFT more often had small airway involvement, and (iii) impairment of PFT was related to the activity of the disease.

Patients with UC are known to have several extraintestinal manifestations including pulmonary involvement. Douglas *et al.*²⁶ found PFT abnormalities in 32% of patients with UC. However, most of the patients in their study were smokers. In our study, all participants were non-smokers or ex-smokers (3 out of 87) and thus any possible negative impact of smoking on PFT results was negligible. Sethy *et al.*¹⁹ and Tzanakis *et al.*¹⁴ also found deranged PFT in 17% ($n = 85$) and 27% ($n = 51$) patients with UC.

We found that UC patients had significantly lower DLCO as compared with controls. The reduction in DLCO 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 diffusing capacity of the lungs is a common and early manifestation of interstitial lung disease.²⁷ The observed reduction in DLCO in our study might well be consistent with the presence of a subclinical alveolitis²⁸ supporting the hypothesis of the migration of an inflammation via the bloodstream, from the intestine into both lung parenchyma and airway mucosa.²⁹

Table 2 Demographic, clinical, and laboratory parameters of ulcerative colitis patients with abnormal and normal PFT

Parameters	PFT abnormal (n = 24)	PFT normal (n = 63)	P-value
Age (years), median (range)	36 (18–56)	41 (16–66)	0.677
Sex (males), n (%)	16 (66.6)	39(64.9)	0.805
Median duration of disease (months)	48 (1–180)	48 (6–240)	0.426
Extent of disease			
Proctitis (%)	3 (12.5)	21 (33.3)	0.06
Left-sided colitis (%)	15 (62.5)	27 (42.9)	0.149
Pancolitis (%)	6 (25)	15 (23.8)	0.908
Severity of disease			
Remission (%)	9 (37.5)	40 (63.5)	0.033
Active (%)	15 (62.5)	23 (36.5)	0.033
Mild (%)	1 (4.2)	5 (7.9)	0.371
Moderate (%)	5 (20.8)	4 (6.3)	0.444
Severe (%)	9 (37.5)	14 (22.2)	0.773
BMI (kg/m ²)	23.05 (15.9–34.9)	20.8 (14.8–34.2)	0.784
Albumin (mg/dL)	3.75 (1.7–4.8)	3.9 (1.6–4.9)	0.604
Hemoglobin (g/dL)	11 (6.7–15.3)	11.8 (5.3–17.2)	0.409
Treatment of the disease			
5-ASA	21	57	0.475
Salazopyrine	3	6	0.475
Azathioprine	4	12	0.533
Methotrexate	0	2	0.522

Mann–Whitney *U*-test for continuous data and chi-square test for categorical data. All continuous data are presented as median and range. For categorical data, figures within parenthesis indicate percentages

ASA, amino salicylic acid; BMI, body mass index; PFT, pulmonary function test.

Table 3 Clinical profile of patients in remission and active colitis

Parameters	Remission (n = 49)	Active colitis (n = 38)	P-value
Age (years), median (range)	40 (16–62)	37(16–66)	0.768
Sex (males), n (%)	33 (67.3)	22(57.9)	0.380
Mean duration of disease (months)	48 (6–280)	36 (1–240)	0.548
Abnormal PFT, n (%)	9(18.4)	15 (39.5)	0.033
Obstructive pattern, n (%)	0	1 (6.7)	1.000
Small airway disease, n (%)	7 (77.8)	5 (33.3)	0.089
Restrictive pattern, n (%)	2 (22.2)	9 (60)	0.105
FEV ₁ (%), median (range)	89 (54–171)	86.5 (51–124)	0.504
FEV ₁ /FVC (%), median (range)	84 (66–120)	88 (63–100)	0.779
FVC (%), median (range)	87 (65–145)	83 (49–128)	0.271
MEF _{25–75} (%), median (range)	77 (24–176)	77.5 (33–135)	0.745
PEFR median (%) (range)	82 (49–122)	75.5 (38–108)	0.086
DLCO (%), median (range)	112 (80–213)	105 (68–143)	0.221
MEF25 (%), median (range)	69 (23–261)	63.5 (33–138)	0.784
MEF75 (%), median (range)	81 (25–131)	76 (35–140)	0.346
BMI (kg/m ²)	21.8 (15.4–34.2)	19.5 (14.8–29.5)	0.057
Hemoglobin (g/dL)	12.9 (5.3–17.2)	10.6 (6.7–13.8)	0.000
Albumin (g/dL)	4 (2.1–4.9)	3.35 (1.6–4.5)	0.000

Mann–Whitney *U*-test for continuous data and chi-square test for categorical data. All continuous data are presented as median and range. For categorical data, figures within parenthesis indicate percentages.

BMI, body mass index; DLCO, diffusion lung capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mean expiratory flow; PEFR, peak expiratory flow rate; PFT, pulmonary function test.

Small airway function (decreased MEF_{25–75}) was significantly impaired in patients with UC as compared with controls in our study. Tzanakis *et al.*⁵ found alteration in the function of

small airways independent of the presence of atopy in patients with UC even without pulmonary symptoms. Mild airway inflammation, secondary to the primary inflammation of the intestinal

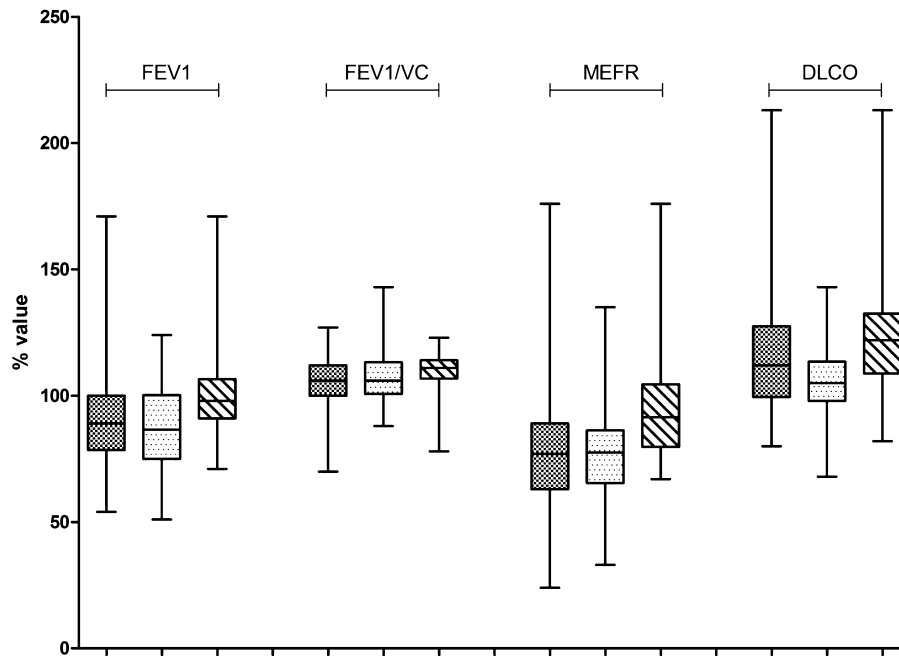


Figure 1 FEV₁, FEV₁/FVC, MEFR, and DLCO in patients with remission (▨), relapse (□), and control (■). FEV₁ ([remission vs controls, $P = 0.003$], [relapse vs controls, $P = 0.001$] and [remission vs relapse, $P = 0.504$]). FEV₁/FVC ([remission vs controls, $P = 0.005$], [relapse vs controls, $P = 0.049$] and [remission vs relapse, $P = 0.595$]). MEFR ([remission vs controls, $P = 0.00$], [relapse vs controls, $P = 0.00$] and [remission vs relapse, $P = 0.745$]). DLCO ([remission vs controls, $P = 0.007$], [relapse vs controls, $P = 0.002$] and [remission vs relapse, $P = 0.784$]). DLCO, diffusion lung capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MEFR, mid-expiratory flow rate.

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.³⁰

All UC patients, whether active or in remission, had abnormal PFT as compared with healthy subjects in our study. Thus, it may suggest that patients, even after remission of UC, may continue to have deranged PFT. Also, in our study, FEV₁, FEV₁/FVC, MEFR, and DLCO were significantly decreased in patients with active or inactive disease as compared with controls. Patients with active disease had lower PEFR and DLCO than in inactive disease, although not statistically significant. Herrlinger *et al.*¹¹ and Mohamed-Hussein¹³ also found that FEV₁ and FVC significantly decreased in patients with active disease as compared to those with an inactive disease. In another study, Fehmi *et al.*¹⁵ found significantly decreased FEV₁, FVC, and DLCO when PFT in the active and in remission phases in the same patient was compared with control.

Among the patients with deranged PFT, 1 (4.2%) had obstructive, 12 (50%) had small airway disease and 11 (45.8%) had a restrictive pattern of lung involvement. Sethy *et al.*²¹ reported restrictive pattern and small airway disease in 16% and 8% of UC patients ($n = 51$) with abnormal PFT. Godet *et al.*⁹ 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. 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.³¹ Our results are somewhat in accordance with that study.³¹

A higher number of patients with disease limited to rectum had normal PFT (33.3% vs 12.5%; $P = 0.06$) in our study. This can be explained by higher chances of lung involvement by an inflammatory process as the extent of UC increases from rectum to the whole colon. Data on the relationship between the extent of UC and PFT abnormalities are scanty in the literature. Hence, more studies with higher number of patients are needed to know the influence of disease extent on pulmonary functions.

In contrast to our study that showed a lack of relationship between BMI and PFT results, Herrlinger *et al.* found weak correlation between inspiratory vital capacity ($r = 0.25$, $P < 0.05$) and BMI but not for FEV₁ ($r = 0.18$, $P < 0.89$) and DLCO ($r = 0.24$, $P < 0.20$).³

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.

We conclude that about one-fourth of patients with UC have abnormal PFT. The impairment of pulmonary functions correlates with the activity of the disease. Pathophysiological mechanisms and clinical relevance need to be studied further.

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