ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

Alterations in the pulmonary function tests of inflammatory bowel diseases

Fehmi ATEŞ[1], Melih KARINCAOĞLU[2], Süleyman Savaş HACIEVLİYAGİL[3], Mehmet YALNIZ[4], Yüksel SEÇKİN[2]

Department of [1]Gastroenterology, Mersin University School of Medicine, Mersin
Departments of [2]Gastroenterology and [3]Chest Diseases, İnönü University School of Medicine, Malatya
Department of Gastroenterology, Fırat University School of Medicine, Elazığ

Background/aims: *We aimed to determine the changes in the pulmonary function tests of the patients with inflammatory bowel diseases.* ***Methods:*** *Forty inflammatory bowel dieases patients; 30 ulcerative colitis and 10 Crohn's disease, and age- and sex-matched control group, consisting of 30 healthy persons, were included in the study. Disease activity in patients with ulcerative colitis was assessed by Truelove and Witts Criteria and in Crohn's disease patients by Chron's Disease Activity Index.* ***Results:*** *Pulmonary function tests were found abnormal at least in one parameter in 17/30 ulcerative colitis patients (56%) and in 5/10 Crohn's disease patients (50%) in the activation period and in 5/30 ulcerative colitis patients (17%) and in 2/10 Crohn's disease patients (20%) in the remission period of the diseases of the same patients. Forced vital capacity, first second, residual volume/total lung capacity, diffusing capacity of the lung for carbon monoxide and diffusing capacity of the lung for carbon monoxide per liter alveolar volume values were found significantly impaired in the activation period in comparison with the values of the same patients in the remission period ($p<0.01$). It was found that pulmonary function test values in patients with inflammatory bowel dieases were not affected by either the type of disease or treatment with 5-aminosalicylic acid. However, they were affected notably by the disease activity.* ***Conclusion:*** *Pulmonary function test abnormalities were found frequently in patients with inflammatory bowel dieases without presence of any respiratory symptoms and lung radiograph findings. The severity and frequency of these pulmonary function test abnormalities which were detected even in the remission periods increase with the activation of the disease. Therefore, pulmonary function test may be used as a non-invasive diagnostic procedure in determining the activation of inflammatory bowel dieases and might aid to the early diagnosis of the latent respiratory*

Key words: Inflammatory bowel diseases, pulmonary function tests, carbon monoxide diffusion test

İnflamatuvar bağırsak hastalıklarında görülen solunum fonksiyon testlerindeki değişiklikler

Amaç: *Bu çalışmada inflamatuvar barsak hastalarında, solunum fonksiyon testi değişikliklerinin araştırılması amaçlanmıştır.* ***Yöntem:*** *Çalışmaya, 30'u ülseratif kolit, 10'u Crohn hastalığı olan toplam 40 inflamatuvar bağırsak hastası ve 30 sağlıklı bireyden oluşan kontrol grubu alındı. Ülseratif kolit ve Crohn hastaları ile kontrol grubunun yaş ve cinsiyet dağılımları benzerdi. Ülseratif kolit hastalarında hastalık aktivitesi Truelove-Witts Kriterleri ile Crohn hastalarında hastalık aktivitesi Crohn hastalığı aktivite indeksi ile değerlendirildi. Tüm hastalarda solunum fonksiyon testi remisyon ve aktivasyon dönemlerinde uygulandı.* ***Bulgular:*** *Aktivasyon dönemlerinde 30 ülseratif kolit hastasının 17'sinde (%56) ve 10 Crohn hastasının 5'inde (%50) en az bir parametrede olmak üzere solunum fonksiyon testi anormalliği saptandı. İnflamatuvar bağırsak hastalığının aktivasyon dönemindeki hastaların zorlu vital kapasite, birinci saniyedeki zorlu vital kapasite, rezidüel volüm/toplam akciğer kapasitesi, difüzyon kapasitesi ve her bir litre akciğer volümüne düşen difüzyon kapasitesi değerleri aynı hastaların remisyon dönemindeki değerlerine göre anlamlı derecede bozuk bulundu (hepsi için $p<0.01$). İnflamatuvar bağırsak hastalığında görülen solunum fonksiyon testi anormalliklerinin hastalık türünden (ülseratif kolit veya Crohn hastalığı) ve 5-aminosalisilik asit tedavisinden (alıyor veya almıyor) etkilenmediği ancak hastalık aktivitesinden (aktif veya remisyonda) anlamlı derecede etkilendiği belirlendi.* ***Sonuç:*** *İnflamatuvar bağırsak hastalığında, solunumsal semptom ve akciğer grafisi bulgusu olmadan solunum fonksiyon testi bozuklukları gelişebilir. İnflamatuvar bağırsak hastalığının aktivasyon döneminde solunum fonksiyon testi anormalliklerinin şiddet ve sıklıkları artmaktadır. Bu nedenle solunum fonksiyon testi, inflamatuvar bağırsak hastalığının non invaziv aktivasyon belirleyicilerinden biri olarak kullanılabilir ve latent solunum sistemi hastalıklarına erken tanı konulmasını sağlayabilir.*

Anahtar kelimeler: İnflamatuvar bağırsak hastalığı, solunum fonksiyon testleri, karbon monoksit diffüzyon testi

Address for correspondence: Fehmi ATEŞ
Mersin University School of Medicine,
Department of Gastroenterology, Mersin, Turkey
Phone: + 90 324 337 43 00
E-mail: drfehmiates@hotmail.com

Manuscript received: 24.06.2010 **Accepted:** 01.09.2010

Turk J Gastroenterol 2011; 22 (3): 293-299
doi: 10.4318/tjg.2011.0215

INTRODUCTION

Though inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD) are primarily colonic and small intestinal diseases, they are considered as systemic diseases because they result in disorders in other organs and tissues. Skin, mucosa, joints, bone, eye, kidney, liver, pancreas, and lungs are the principal tissues and organs that are known to be affected by IBD.

Several respiratory diseases, such as small and large airway disorders (1,2), obstructive and interstitial lung diseases (3), increase in bronchial sensitivity (4), bronchitis, bronchiectasis (5-8), inflammatory tracheal stenosis (9), interstitial pneumonitis (10), and bronchiolitis obliterans (11-13) have been reported in patients with IBD. However, information about the types and incidence of respiratory disorders associated with IBD are insufficient.

There are various studies that have revealed the relationship between respiratory disorders and IBD activity (14,15). Furthermore, side effects of the drugs used in the treatment of IBD may also contribute to the occurrence of respiratory findings. Aminosalicylate (ASA) agents (16,17) are the primary drugs used in the treatment of acute attacks in IBD and in maintenance treatment in the remission period (18-24). It has been reported that hypersensitivity pneumonitis may develop rarely during sulfasalazine or mesalazine treatment (25-29).

In most of the studies that investigated the impacts of IBD on the respiratory system, pulmonary function tests (PFTs) were used. Although in some studies, no difference regarding PFT values was found between the IBD group and control group (30,31), it was found that in some patients, especially in the patients with active IBD, diffusing capacity of the lung for carbon monoxide (DLCO) decreased (1,15,32).

In this study, we aimed to investigate the changes in PFTs in IBD patients without any respiratory system disease history, symptoms or pathological lung X-ray findings and to determine the relationship between such changes and the type and activity of the diseases and ASA treatment.

MATERIALS AND METHODS

Patients

Thirty patients with UC and 10 patients with CD (totally 40 patients with IBD) under the investigation of Inonu University Medical Faculty Gastroenterology Clinic and 30 healthy controls were recruited in this study. The patients were 18-68 years old, with a mean age of 40±12 years. The individuals in the control group were 18-63 years old, with a mean age of 41±11 years. All patients were diagnosed on the basis of their history, clinical – endoscopic findings and pathological reports of their endoscopic biopsy samples. The duration of the disease was defined as the period between the date of pathological diagnosis and the date of PFT. The duration range was from 1 month to 362 months, and the mean duration was 90±85 months. Age and gender distributions in the UC group, CD group and control group were similar. Durations of disease in UC and CD patients were comparable (Table 1). The patients included in the study within the activation period of their disease were assessed again 3 months after the clinical remission, thus aiming to minimize the impact of the factors that may affect the PFT in the activation period. Twenty of 30 UC patients (66.6%), 7 of 10 CD patients (70%) and in total 27 of 40 IBD patients (67.5%) received ASA within the activation period. In the remission period, 18 of 30 UC patients (60%) and 5 of 10 CD patients (50%) and in total 23 of 40 IBD patients (57.5%) were using 2-4 mg/day ASA for at least 5 days. The patients who received 5-ASA for longer than five days were defined as ASA user and the remaining were considered as the non-ASA user group. The patients had to be receiving ASA within the 7 days before the date of the PFT in order to be included in the ASA user group. None of the patients received methotrexate, azathioprine, corticosteroids, or infliximab treatment.

Exclusion Criteria

Patients who underwent major surgical operations and those with pathological findings on their direct lung radiographs, infectious bronchitis and pneumonitis, occupational lung disease, smoking ha-

Table 1. Characteristics of the patient and control groups

	UC	CD	Control
n	30	10	30
Gender (male/female)	14/16	5/5	15/15
Mean age (year)	40±13	38±8	41±11
Duration of disease (month)	93±95	79±40	-
Aminosalicylate (%) *	63	60	-

* % of the patients who received aminosalicylate was calculated as the sum of activation and remission periods. Data show average ± standard deviation.

UC: Ulcerative colitis. CD: Crohn's disease

bit, collagen tissue disease, and obesity (body mass index [BMI] >30 kg/m^2) were excluded from the study since PFT may be affected by those conditions. Patients with known chronic lung disease or heart disease, who received drugs that may affect PFT (e.g. non-steroidal anti-inflammatory drugs or angiotensin converting enzyme inhibitors), and those noncompliant with PFTs were also excluded from the study, as were patients who did not experience a three-month remission period.

Disease Activity

The disease activity in patients with UC was assessed by Truelove and Witts criteria (33), according to which the patients were grouped as mild, moderate or severe based on their feces frequency, presence of blood in their feces, fever, tachycardia, anemia, and increase in sedimentation level. The patients in the moderate and severe group were considered to be in the activation period, whereas the patients in the mild group were considered to be in the remission period.

The disease activity was assessed by CD activity index (CDAI) in patients with CD (34). Using this index, the number of liquid or soft defecations within the last week, abdominal pain or cramping frequency, good health status, number of non-intestinal symptoms, drug use for diarrhea, presence of an abdominal mass, hematocrit values, and body weight/standard weight scores were calculated. The patients with scores >150 were considered to be in the activation period.

Pulmonary Function Tests

All participants were tested by standard PFT. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC, forced expiratory flow$_{25–75\%}$ ($FEF_{25-75\%}$), total lung capacity (TLC), residual volume (RV), RV/TLC, functional residual capacity (FRC), DLCO, and DLCO per liter alveolar volume (DLCO/VA) were measured. DLCO was measured using the single breath method, whereas PFT was measured by a spirometer (Vmax 22 Sensor Medics, Yorba Linda, CA, USA) in accordance with the criteria of the American Thoracic Society (35).

Pulmonary function test changes in IBD were evaluated by comparing PFT values of the patients with those of the healthy control group. The relationship between the PFT changes and type/activity of IBD and ASA treatment was investigated.

Before inclusion, all the patients were informed and their written consents were obtained. The study protocol was approved by the Ethics Committee of the Medical Faculty of Inonu University.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) 13.0. It was determined that the groups showed normal distribution in Kolmogorov-Smirnov test. The independent group Student-t test and one way analysis of variance were used. The values were presented as average ± standard deviation, and $p<0.05$ was accepted to be statistically significant.

RESULTS

Pulmonary function test was abnormal in at least one parameter within the activation periods in 17 of 30 UC patients (56.7%) and in 5 of 10 CD patients (50%). In the remission periods, PFT was abnormal in at least one parameter in 5 of 30 UC patients (16.7%) and in 2 of 10 CD patients (20%). PFT abnormalities were detected in at least one parameter. RV, RV/TLC and FRC values were higher and all the other PFT values were lower in both the activation and remission periods of the IBD patients in comparison with the values of the control group.

Forced vital capacity (FVC), FEV_1, RV, RV/TLC, DLCO, and DLCO/VA values were found statisti-

Table 2. PFT values of the IBD patients in the active period and of the control group

	Active IBD N=40	Control N=30	p
FVC	85.8±5.2	96.7±7.3	**<0.01**
FEV_1	86.6±9.5	97.5±9.4	**<0.01**
FEV_1/FVC	84.2±8.6	84.4±8.5	>0.05
FEF_{25-75}	84.9±5.1	87.7±8.3	>0.05
TLC	95.4±7.1	98.1±6.4	>0.05
RV	114.8±5.6	110.2±6.3	**<0.01**
RV/TLC	39.3±6.3	33.9±5.4	**<0.01**
FRC	105.3±6.8	103.7±8.2	>0.05
DLCO	80.0±6.1	98.7±5.9	**<0.01**
DLCO/VA	80.0±6.3	99.4±6.0	**<0.01**

PFT values were expressed as % of the normal values, predicted according to gender, age, height and weight of the patients, and indicated as average ± standard deviation.

FVC: Forced vital capacity. FEV_1: First second.
FEV_1/FVC: First second/Forced vital capacity.
FEF_{25-75}: Forced expiratory flow$_{25–75\%}$. TLC: Total lung capacity.
RV: Residual volume. RV/TLC: Residual volume/Total lung capacity.
FRC: Functional residual capacity.
DLCO: Diffusing capacity of the lung for carbon monoxide.
DLCO/VA: Diffusing capacity of the lung for carbon monoxide per liter alveolar volume.

cally significantly different in the activation period of the IBD patients compared to the results of the control group (Table 2) ($p<0.01$ for all). No statistically significant difference was found between other PFT parameters of the groups ($p>0.05$ for all).

When the PFT results of the patients in the remission period were compared with the results of the control group, significant differences were found only in the DLCO and DLCO/VA values ($p<0.05$ and $p<0.01$, respectively). No statistically significant difference was found between the other PFT parameters of the groups ($p>0.05$ for all) (Table 3).

Forced vital capacity (FVC), FEV_1, RV/TLC, DLCO, and DLCO/VA values of the patients within the activation period of IBD compared with the results of the same patients in the remission period were significantly different ($p<0.01$ for all). No statistically significant difference was found in the other PFT parameters between the activation vs. remission periods ($p>0.05$ for all) (Table 4).

Pulmonary function test values of the UC and CD patients were comparable in both the activation period ($p>0.05$ for all) and the remission period ($p>0.05$ for all).

When the patients who received 5-ASA treatment were compared with the patients who did not receive 5-ASA treatment, no significant difference was found among the PFT values in either the activation period of IBD or the remission period of IBD ($p>0.05$ for all).

Influences of the type of disease (UC or CD), disease activity (active or in remission) and the ASA treatment (received or not received) on FVC, FEV_1, RV/TLC, DLCO, and DLCO/VA values were investigated using one way analysis of variance. The type of disease and ASA treatment had no influence on them ($p>0.05$ for all). However, the disease activity affected FVC, FEV_1, RV/TLC, DLCO, and DLCO/VA values ($p<0.01$, $p<0.01$, $p<0.05$, $p<0.01$, and $p<0.01$, respectively).

Forced vital capacity (FVC), FEV_1, DLCO, and DLCO/VA distribution values were highest in the control group, lower in the remission group and lowest in the activation group. In contrast, for RV/TLC, the lowest values were found in the control group, higher values in the remission group and the highest values in the activation group.

DISCUSSION

The PFT abnormalities that occur in IBD emerge without any obvious symptom or pathological lung X-ray findings of a respiratory system disease. This result reveals the importance of PFT in detecting latent respiratory system diseases in IBD. In the present study, PFT abnormalities were found in at least one parameter, at ratios of 55% in the activation period and 17.5% in the remission period of IBD. This finding suggests that although pulmonary function disorders increase in the activation period of IBD, they also continue in the remission period. Decreases in DLCO and DLCO/VA values were the most frequent PFT abnormalities in both the activation and remission periods of IBD. This finding reveals that alveolar gas exchange disorders develop frequently in IBD. PFT abnormalities were also assessed separately in UC

Table 3. PFT values of the IBD patients in the remission period and of the control group

	IBD in remission N=40	Control N=30	p
FVC	94.7±7.3	96.7±7.3	>0.05
FEV_1	96.9±7.1	97.5±9.4	>0.05
FEV_1/FVC	83.9±9.4	84.4±8.5	>0.05
FEF_{25-75}	85.4±7.1	87.7±8.3	>0.05
TLC	97.5±7.1	98.1±6.4	>0.05
RV	112.8±6.3	110.2±6.3	>0.05
RV/TLC	35.2±6.5	33.9±5.4	>0.05
FRC	103.9±6.7	103.7±8.2	>0.05
DLCO	94.4±9.0	98.7±5.9	<0.05
DLCO/VA	92.2±6.4	99.4±6.0	<0.01

PFT values were expressed as % of the normal values, predicted according to gender, age, height and weight of the patients, and indicated as average ± standard deviation.

Table 4. PFT values of the IBD patients in the remission and activation periods

	Active IBD N=40	IBD in remission N=40	p
FVC	85.8±5.2	94.7±7.3	**<0.01**
FEV_1	86.6±9.5	96.9±7.1	**<0.01**
FEV_1/FVC	84.2±8.6	83.9±9.4	>0.05
FEF_{25-75}	84.9±5.1	85.4±7.1	>0.05
TLC	95.4±7.1	97.5±7.1	>0.05
RV	114.8±5.6	112.8±6.3	>0.05
RV/TLC	39.3±6.3	35.2±6.5	**<0.01**
FRC	105.3±6.8	103.9±6.7	>0.05
DLCO	80.0±6.1	94.4±9.0	**<0.01**
DLCO/VA	80.0±6.3	92.2±6.4	**<0.01**

PFT values were expressed as % of the normal values, predicted according to gender, age, height and weight of the patients, and indicated as average ± standard deviation.

and CD patients and were found comparable in both the activation period and the remission period. No significant difference was found between the PFT values of the UC patients and the CD patients in either the activation period or remission period.

Many studies have investigated the impacts of IBD on the lungs using PFT. Douglas JG et al. (36) found several PFT abnormalities in 32% of the patients with IBD, and reported that there was a decrease in DLCO values in 16% of the patients. However, this study is criticized because most of the patients were smokers and smoking also results in PFT abnormalities without causing any apparent respiratory diseases. In our study, all participants were selected among non-smoker patients and thus any possible negative impacts of smoking on PFT results were eliminated, and this allowed us to interpret the results more accurately. Similar to our results, Kuzela L et al. (32) also found a decrease in DLCO values by 56.7% in UC patients and by 57.7% in CD patients and asserted that this may be an early predictor of interstitial lung diseases, of which clinical and radiological findings have not yet emerged.

A lower decrease (17%) in DLCO values of the patients with UC was reported by Tzanakis et al. (37), and it was shown that the severity and frequency of PFT changes increase within the activation period. Similar results were also found in pediatric patients with CD (15). In another study, latent lung involvement with PFT abnormalities in 53% of the UC patients reached 81% in the activation period of the disease (38). A strong correlation between the decrease in DLCO - DLCO/VA values and histopathological status of UC has led to the assertion that the decrease in DLCO may be one of the noninvasive predictors for the activation of UC.

Herrlinger KR et al. (39) also found that respiratory disorders were frequent in IBD in both the active and remission periods, with a decreasing severity in parallel to the degree of improvement in the disease activity. Although our study design resembles the study of Herrlinger KR et al., they compared PFT values of different patients with activation and remission periods of IBD. In our study, the values in the activation and remission periods of the same patients were compared. In this way, the individual factors that may affect the PFT values were avoided. Furthermore, in the study of Herrlinger KR et al., only FEV_1, FVC, FEV_1/FVC, and DLCO were assessed. However, in our study, $FEF_{25-75\%}$, RV, TLC, RV/TLC, FRC, and DLCO/VA parameters were assessed in addition to those parameters. In line with our findings, no difference was found between the PFT values of UC and CD patients, and 5-ASA treatment did not affect the PFT values. There are a few cases in the literature presenting pneumonia associated with mesalamine treatment (25,27). Our study, however, suggests that the lung toxicity associated with ASA use is a very rare complication, as reported in the other studies (39,40).

Today, the impact of IBD activity on PFT remains controversial. Whereas in some previous studies, it was indicated that the disease activity did not affect PFT (41,42), in recent studies, significant decreases especially in DLCO values in the activation period of the disease were observed (1,15). Though our study supports the previous studies, which claim that the decrease in DLCO is one of the indicators of IBD activation, it reveals that the disease activity results in significant decreases also in the FVC, FEV_1, RV/TLC, and DLCO/VA values. The decrease in FEV_1 and FVC values without FEV_1/FVC change in the activation period of IBD suggests subclinical restrictive pattern development, and the increase in RV/TLC values without a significant change in TLC suggests occurrence of the diseases such as emphysema, which decrease the lung elasticity. Significantly low DLCO and DLCO/VA values found in the activation and remission periods of IBD patients in comparison with the values of the control group suggest that alveolocapillary membrane function and alveolar gas exchange are impaired in these patients. These impairments, which are more severe and more frequent in the activation period, continue in the remission period.

It may be wondered whether the abnormalities in PFT values of the patients in the activation period of IBD are an extraintestinal finding of the disease or a misleading condition, resulting from poor health condition and weakness of the patients. Therefore, patients who were considered unsuitable for our study were excluded, and this issue was avoided. The low PFT values of the patients, even under better health conditions in the remission period, support the opinion that the lungs are one of the target organs in IBD.

The pathogenesis of PFT abnormalities observed in IBD is still unclear. It is believed that the morphological and developmental similarities between colonic and bronchial tissues may have a role in the

development of PFT abnormalities. The origin of both tissues is primitive intestine, and both tissues include columnar epithelium, goblet cells and submucosal mucus glands (43). On the other hand, the cytokines such as interleukin (IL)-1, IL-2, IL-6, and tumor necrosis factor (TNF)-α, released from the activated inflammatory cells, may also cause systemic findings. It is known that the cytokines result in a kind of interstitial pneumonia in the lungs. It is also known that the lung inflammation in IBD causes subclinical alveolitis and/or interstitial lung disease (44,45). Consequently, it is believed that microcirculation in the lungs and alveolocapillary membrane functions are affected by this pathological process, and alveolar gas exchange is impaired.

In this study, we found that PFT abnormalities may develop in IBD without presence of any obvious respiratory symptoms or lung X-ray findings. PFT abnormalities increase in the activation period of IBD, and FVC, FEV_1, RV/TLC, DLCO, and DLCO/VA values of the patients are significantly different in the activation and remission periods. These findings are important for using PFT as one of the noninvasive diagnostic procedures in determining IBD activation and in the early diagnosis of possible respiratory system diseases.

REFERENCES

1. Tzanakis N, Samiou M, Bouros D, et al. Small airways function in patients with inflammatory bowel disease. Am J Respir Crit Care Med 1998; 157: 382-6.
2. Spira A, Grossman R, Balter M. Large airway disease associated with inflammatory bowel disease. Chest 1998; 113: 1723-6.
3. Camus P, Piard F, Ashcroft T, et al. The lung in inflammatory bowel disease. Medicine (Baltimore) 1993; 72: 151-83.
4. Mansi A, Cucchiara S, Greco L, et al. Bronchial hyperresponsiveness in children and adolescents with Crohn's disease. Am J Respir Crit Care Med 2000; 161: 1051-4.
5. Kraft SC, Earle RH, Roesler M, et al. Unexplained bronchopulmonary disease with inflammatory bowel disease. Arch Intern Med 1976; 136: 454-9.
6. Iwama T, Higuchi T, Imajo M, et al. Tracheo-bronchitis as a complication of Crohn's disease. A case report. Jpn J Surg 1991; 21: 454-7.
7. Eaton TE, Lambie N, Wells AU. Bronchiectasis following colectomy for Crohn's disease. Thorax 1998; 53: 529-31.
8. Mahadeva R, Walsh G, Flower CD, et al. Clinical and radiological characteristics of lung disease in inflammatory bowel disease. Eur Respir J 2000; 15: 41-8.
9. Kuzniar T, Sleiman C, Brugiere O, et al. Severe tracheobronchial stenosis in a patient with Crohn's disease. Eur Respir J 2000; 15: 209-12.
10. Le Roux P, Boulloche J, Briquet MT, et al. Respiratory manifestation of Crohn's disease. Apropos of a case in an adolescent. Rev Mal Respir 1995; 12: 59-61.
11. Mahajan L, Kay M, Wyllie R, et al. Ulcerative colitis presenting with bronchiolitis obliterans organizing pneumonia in a pediatric patient. Am J Gastroenterol 1997; 92: 2123-4.
12. Baron FA, Hermanne JP, Dowlati A, et al. Bronchiolitis obliterans organizing pneumonia and ulcerative colitis after allogeneic bone marrow transplantation. Bone Marrow Transplant 1998; 21: 951-4.
13. Bentur L, Lachter J, Koren I, et al. Severe pulmonary disease in association with Crohn's disease in a 13-year-old girl. Pediatr Pulmonol 2000; 29: 151-4.
14. Pasquis P, Colin R, Denis P, et al. Transient pulmonary impairment during attacks of Crohn's disease. Respiration 1981; 41: 56-9.
15. Munck A, Murciano D, Pariente R, et al. Latent pulmonary function abnormalities in children with Crohn's disease. Eur Respir J 1995; 8: 377-80.
16. Ludwig D, Stange EF. Treatment of ulcerative colitis. Hepatogastroenterology 2000; 47: 83-9.
17. Sands BE. Medical therapy of steroid-resistant Crohn's disease. Can J Gastroenterol 2000; 14(Suppl): 33C-7C.
18. Brimblecombe R. Mesalazine: a global safety evaluation. Scand J Gastroenterol Suppl 1990; 172: 66.
19. Averbuch M, Halpern Z, Hallak A, et al. Sulfasalazine pneumonitis. Am J Gastroenterol 1985; 80: 343-5.
20. Sebastian Domingo JJ, Ventura A, Perez de Alaya V, et al. Hypersensitivity pneumonitis by sulfasalazine. Allergy 1989; 44: 522.
21. Yaffe BH, Korelitz BI. Sulfasalazine pneumonitis. Am J Gastroenterol 1983; 78: 493-4.
22. Leino R, Liippo K, Ekfors T. Sulphasalazine-induced reversible hypersensitivity pneumonitis and fatal fibrosing alveolitis: report of two cases. J Intern Med 1991; 229: 553-6.
23. Kolbe J, Caughey D, Rainer S. Sulphasalazine-induced subacute hyper-sensitivity pneumonitis. Respir Med 1994; 88: 149-52.
24. Peters FP, Engels LG, Moers AM. Pneumonitis induced by sulphasalazine. Postgrad Med J 1997; 73: 99-100.
25. Bitton A, Peppercorn MA, Hanrahan JP, et al. Mesalamine-induced lung toxicity. Am J Gastroenterol 1996; 91: 1039-40.
26. Pascual-Lledo JF, Calvo-Bonachera J, Carrasco-Miras F, et al. Interstitial pneumonitis due to mesalamine. Ann Pharmacother 1997; 31: 499.
27. Sviri S, Gafanovich I, Kramer MR, et al. Mesalamine-induced hypersensitivity pneumonitis. A case report and review of the literature. J Clin Gastroenterol 1997; 24: 34-6.
28. Ogino H, Tachibana Y, Yonejima H, et al. A case of ulcerative colitis associated with interstitial pneumonitis during administration of 5-aminosalicylic acid. Nippon Shokakibyo Gakkai Zasshi 1999; 96: 164-9 (in Japanese).
29. Zamir D, Weizman J, Zamir C, et al. Mesalamine-induced hypersensitivity pneumonitis. Harefuah 1999; 137: 28–30, 86-7 (in Hebrew).
30. Johnson NM, Mee AS, Jewell DP, et al. Pulmonary function in inflammatory bowel disease. Digestion 1978; 18: 416-8.
31. Tzanakis N, Bouros D, Samiou M, et al. Lung function in patients with inflammatory bowel disease. Respir Med 1998; 92: 516-22.
32. Kuzela L, Vavrecka A, Prikazska M, et al. Pulmonary complications in patients with inflammatory bowel disease. Hepatogastroenterology 1999; 46: 1714-9.

33. Truelove SC, Witts LJ. Cortisone in ulcerative colitis. Final report in therapeutic trial. Br Med J 1995; 2: 1041-8.
34. Gasche C, Scholmerich J, Byrnskov J, et al. A simple classification of Crohn's disease; report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflam Bowel Dis 2000; 6: 11.
35. American Thoracic Society. Lung function testing. Selection of reference values and interpretative strategies. Am Rev Respir Dis 1991; 144: 1202-18.
36. Douglas JG, McDonald CF, Leslie MJ, et al. Respiratory impairment in inflammatory bowel disease: Does it vary with disease activity? Resp Med 1989; 83: 389-94.
37. Tzanakis N, Bouros D, Samiou M, et al. Lung function in patients with inflammatory bowel disease. Resp Med 1998; 98: 516-22.
38. Marvisi M, Borello PD, Brianti M, et al. Changes in the carbon monoxide diffusing capacity of the lung in ulcerative colitis. Eur Respir J 2000; 16: 965-8.
39. Herrlinger KR, Noftz MK, Dalhoff K, et al. Alterations in pulmonary function in inflammatory bowel disease are frequent and persist during remission. Am J Gastroenterol 2002; 97: 377-81.
40. Brimblecombe R. Mesalazine: a global safety evaluation. Scand J Gastroenterol Suppl 1990; 172: 66.
41. Bonniere P, Wallaert B, Cortot A, et al. Latent pulmonary involvement in Crohn's disease: biological, functional, bronchoalveolar lavage and scintigraphic studies. Gut 1986; 27: 919-25.
42. Eade OE, Smith CL, Alexander JR, et al. Pulmonary function in patients with inflammatory bowel disease. Am J Gastroenterol 1980; 73: 154-6.
43. Cohen M, Sahn SA. Bronchiectasis in systemic disease. Chest 1999; 116: 1063-74.
44. Andus T, Gross V, Casar D, et al. Activation of monocytes during inflammatory bowel disease. Pathobiology 1991; 59: 166-70.
45. Wallaert B, Dugas M, Dansin T, et al. Subclinical alveolitis in immunological systemic disorders. Transition between health and disease. Eur Respir J 1990; 3: 1206-16.