

BRONCHIAL HYPERREACTIVITY IN SARCOIDOSIS PATIENTS: CORRELATION WITH AIRFLOW LIMITATION INDICES

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ABSTRACT. Bronchial hyperreactivity (BHR) in sarcoidosis has been reported in 5 to 83% of patients, but the relationship between BHR and airway functional status being unclear. The aim of the study was to assess the prevalence and degree of BHR in a group of pulmonary sarcoidosis patients and how BHR does relate to the functional status of airways. *Material and methods:* 56 consecutive sarcoidosis outpatients (26 f, 30 m) were included. There were 14 (25%) patients in stage I, 32 (57.1%) patients in stage II and 10 (17.9%) patients in stage III. In all patients the standard evaluation included a history, physical examination, chest radiogram, serum ACE activity and lung function assessment were done. The provocation challenge test with doubling concentrations of histamine was performed in all patients using the standardized protocol recommended by the ERS. *Results:* 4 patients (7%) were restrictive, airway obstruction was detected in 7 (12.5%) cases. Up to 32% of patients had maximal expiratory flows at low lung volumes below the lower limit of normal (LLN). The histamine challenge test results: in 9 cases (16%) the fall in FEV₁ was <20% of the baseline; mean PC₂₀H (n=47) was 5.7 ± 5.9 mg/mL, range: 0.56-26.7 mg/mL. The challenge test was regarded as positive (PC₂₀H ≤ 8 mg/mL) in 71.4% of the group. BHR expressed as ln(PC₂₀H) correlated weakly but significantly with FEV₁, FEV₁%VC, MMEF and PEF. *Conclusion:* BHR occurs frequently in sarcoidosis patients and should be considered especially in patients with airflow limitation. (*Sarcoidosis Vasc Diffuse Lung Dis* 2012; 29: 99-106)

KEY WORDS: sarcoidosis, bronchial reactivity, pulmonary function test, provocation test

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology with the most frequent manifestation in the lungs and intrathoracic lymph nodes, where it is usually diagnosed (1, 2). Although the “restrictive defect”, a reduction in static lung vol-

umes and reduced compliance, and “impaired gas exchange” expressed as reduced transfer factor, is classically considered the most prevalent alteration, airway obstruction may also occurs, and even more frequently than restriction (3). Airways are frequently involved in the disease process, and this is used in establishing a diagnosis (4, 5). Airway obstruction in the course of pulmonary sarcoidosis is reported in 5 to 63% of cases, depending on the different criteria for obstruction (3, 6-13). The presence of airway obstruction is reported to be associated with increased morbidity, respiratory symptoms and mortality risk (14, 15). The causes of airflow limitation in sarcoidosis are various: narrowing of the airways due to either granulomatous lesions or subsequent fibrotic scarring, compression by enlarged lymph nodes, or

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airway distortion attributable to pulmonary fibrosis (7, 9, 16-19). Bronchial hyperreactivity (BHR) may be considered as a potential additional reason for airflow limitation in sarcoidosis patients (8, 11, 20). BHR may explain symptoms like dyspnea, cough and wheezing, even in patients presenting with normal spirometric findings and normal lung parenchyma shown on a chest radiograph (1, 21, 22).

A few authors studied the prevalence of BHR in sarcoidosis patients, and reported discordant results, BHR being reported in 5 to 83% of patients (8, 23-30). This wide range likely reflects different methods of assessing BHR and patient selection. In earlier studies a histologic diagnosis was usually lacking. Another divergence may be also arise from different definitions of BHR, and the use of non-standardized methods.

The purpose of this study was to assess the prevalence and degree of BHR in patients with pulmonary sarcoidosis. We used a well standardized method in a group of patients with nosologically documented disease and after excluding conditions that could affect BHR. The secondary outcome was the relationship between BHR and bronchial patency expressed as indices of airflow lung function.

MATERIAL AND METHODS

Patients

The study group comprised 56 consecutive sarcoidosis patients (26 females, 30 males) in whom we excluded: treatment with corticosteroids during previous 6 months, established diagnosis of asthma, history of atopy or recent pulmonary disease. In 44 (78.7%) cases diagnosis was confirmed by histopathological assessment of a tissue specimen (26 cases from endobronchial biopsy (EBB), 12 cases from mediastinoscopy, 4 cases transbronchial biopsy (TBB), 1 from video assisted thoracoscopy and 1 from open lung biopsy). In 12 cases the clinical feature (including Löfgren's syndrome) and self limitation of the disease with no treatment firmly suggested the diagnosis of sarcoidosis. The mean age was 38.8 ± 8.3 years. There were 14 (25%) patients in stage I, 32 (57.1%) patients in stage II and 10 (17.9%) patients in stage III. There were no patients in stage IV of sarcoidosis. The mean time from the

onset of the disease (presentation of symptoms or positive radiograph and established diagnosis) to the study of BHR was 3.6 ± 5.8 years (median 0.8 year, range 0-20 years). In 51.8% of cases sarcoidosis was diagnosed in the last year (13 cases diagnosed at the time of investigation), in 71.4% the disease within <5 years. The majority of patients were current non-smokers ($n=49$, 87.5%), of whom 16 were ex-smokers; 7 were current smokers, so 23 patients were ever-smokers with a mean exposition to tobacco smoke of 7.0 ± 5.4 pack-years. The study was approved by the Ethics Committee of the National TB & Lung Diseases Research Institute, and each subject gave informed, written consent.

Evaluation

All patients underwent a standard evaluation that included a history, physical examination and concurrently performed: chest radiogram, serum ACE activity and lung function assessment (spirometry and flow-volume curve, whole body plethysmography, static lung compliance, single breath diffusion lung capacity for carbon monoxide; Master-Screen Body – Jaeger, Germany). Data on the medical history of the subjects were collected using a specially designed questionnaire with questions aimed at symptoms of asthma and allergies, smoking habit and ever used treatment for respiratory diseases. Radiographic stages were defined in accordance with the ERS/ATS statement on sarcoidosis (21). Equipment used for investigation had certificates and approvals for clinical investigations. The ERS guidelines for all lung function measurements and predicted values were applied (except the static lung compliance – predicted from Begin *et al.*) (31-34). The lower limits of normal (LLN) were set at the level of 5th percentile for the reference population (33). The results were presented in absolute units, as % predicted and as standardized residuals ($SR = (\text{observed} - \text{predicted})/RSD$).

Bronchial provocation test

The provocation challenge was performed in all patients using the standardized protocol according to Cockcroft recommended by the ERS (32). Equipment used for investigation (ISPA – MES, Poland) had certificates and approvals for clinical investiga-

tions. The test solutions of aerosol were generated using a pressure (350 kPa) driven nebulizer giving 90% particles with MMAD range 1 to 4.9 μm . The mean output was 0.002 mL/s, delivering 0.24 mL for one inhalative phase (2 minutes) as recommended (35). After inhalation of the diluent control solution (saline phosphate buffer without calcium and magnesium ions), doubling concentrations of histamine starting from 0.25 mg/mL were given up to a maximum 32 mg/mL or until the fall in FEV₁ exceeded 20% of baseline. Each patient produced at least three technically satisfactory and superimposable flow-volume curves, delivered 30 seconds up to 120 seconds after each inhalation. Patients who showed a fall in FEV₁ >20% were given salbutamol (400 mcg via spacer) and FEV₁ recovery was documented by spirometry. All provocation tests were performed between 8.00 and 11.00 am. Bronchial hyperreactivity was expressed as the natural logarithm of PC₂₀H.

The results of challenge tests were interpreted according to ERS guidelines, the borderline level being 8 mg/mL (32).

Lung function data were expressed in SR and %pred. as mean value \pm SD. A p-value <0.05 was regarded as significant. Group comparisons were made using Student's t-test for independent samples and analysis of variance tests (ANOVA) for more than two groups. Pearson chi-square test was used for frequency distribution assessment. Statistical analysis was performed using Statistica for Windows (StatSoft, Inc. (2010). STATISTICA (data analysis software system), version 9.1. www.statsoft.com.).

RESULTS

A restrictive ventilatory defect (TLC below LLN) was found in 4 patients (7%), and airway obstruction (FEV₁%VC below LLN) in 7 patients (12.5%). Up to 32% of patients had decreased maximum expiratory flows at low lung volumes. The most frequently detected disturbances were in the static lung compliance (34%) and lung diffusion capacity (35.9%). The functional characteristics relative to disease stage are shown in table 1.

The challenge test was performed in all 56 patients; in 9 cases (16%) the fall in FEV₁ was <20% of baseline, so the PC₂₀H could not be calculated.

Mean PC₂₀H (n=47) was 5.7 ± 5.9 mg/mL, median: 3.76 mg/mL, range: 0.56-26.7mg/mL.

In 40 cases (71.4%) the challenge test was regarded as positive (PC₂₀H \leq 8mg/mL). The mean natural logarithm of PC₂₀H (ln(PC₂₀H)) was 1.28 ± 0.97 , median 1.32, range: -0.58 to 3.29.

The distribution of PC₂₀H results were close to normal (Kolmogorov-Smirnov and Shapiro-Wilk *W* tests), with the maximum value near to 4 mg/mL. There was no significant influence of smoking habits on lung function or on challenge test results, as well, the results did not differ significantly between different stages of disease (ANOVA, $p > 0.05$).

In the majority of cases the spirometric airflow indices were within the normal range, but there was a statistically significant correlation, albeit weak, between the degree of BHR expressed as ln(PC₂₀H) and dynamic airflow indices (FEV₁%VC, FEV₁, PEF, MMEF) (figure 1).

Except for PEF all spirometric indices were significantly better in subjects without BHR compared to those with BHR (table 2).

There was no relationship between the degree of BHR and: lung volumes (VC, TLC, RV, TGV), diffusion lung capacity (D_{L,CO}), static lung compliance (table 2, t-test: $p > 0.05$).

ANOVA revealed no relation between BHR results and smoking status (including ever-never smokers as categorical predictor and packyears as continuous predictor).

DISCUSSION

The lung function measurements in patients with pulmonary sarcoidosis revealed that few of them (7%) presented with volume restriction. This came as a surprise, because 75% of them had parenchymal involvement observed in classic chest radiographs. However, this is in keeping with the literature, the majority of sarcoidosis patients especially in stages I and II being reported as having normal lung volumes (3, 36, 37). Despite the low rate of volume restriction, functional impairment expressed as lowered static lung compliance and diminished diffusion capacity for carbon monoxide occurred frequently (in one third) of patients. This corroborates the reported high sensitivity of D_{L,CO} and C_{L,st} tests in detecting lung function impairment in sarcoidosis patients (3, 21, 38-40).

Table 1. Characteristic of the patients with sarcoidosis in different stages of the disease. Lung function indices are expressed as standardized residuals (SR) and % of predicted value (with exception of the total airway resistance and PC₂₀H). The frequencies of abnormal results were counted in subgroups

Patients in stage:		I	II	III	all
N (% of all):		14 (25%)	32 (57%)	10 (18%)	56 (100%)
Active smokers (ex-smokers)		0 (3)	7 (8)	0 (5)	7 (16)
Time of the disease (years):		1.6 ± 2.9	2.4 ± 4.4	10.1 ± 7.0	3.6 ± 5.7
TLC	SR	0.15 ± 1.27	0.17 ± 1.25	0.13 ± 1.63	0.16 ± 1.3
	%pred. (% abnormal)	102.06 ± 13.48 (7.1)	102.07 ± 13.84 (9.4)	101.13 ± 17.11 (0.0)	101.9 ± 14.1 (7.1)
VC	SR	0.37 ± 1.26	0.31 ± 1.17	0.34 ± 1.44	0.33 ± 1.22
	%pred. (% abnormal)	104.72 ± 14.82 (7.1)	103.99 ± 14.52 (3.1)	104.47 ± 16.94 (10.0)	104.3 ± 14.8 (5.4)
FEV ₁ %VC	SR	-0.14 ± 0.67	-0.32 ± 1.13	-1.15 ± 1.58	-0.42 ± 1.16
	%pred. (% abnormal)	98.78 ± 5.47 (0.0)	97.25 ± 9.7 (12.5)	90.16 ± 13.18 (30.0)	96.4 ± 9.9 (12.5)
FEV ₁	SR	0.15 ± 1.02	-0.06 ± 1.17	-0.71 ± 0.93	-0.13 ± 1.12
	%pred. (% abnormal)	101.77 ± 12.86 (7.1)	98.69 ± 14.92 (9.4)	90.9 ± 11.55 (10.0)	98.1 ± 14.1 (8.9)
MMEF	SR	-0.59 ± 0.86	-0.75 ± 1.54	-1.72 ± 0.9	-0.89 ± 1.34
	%pred. (%abnormal)	85.28 ± 21.34 (21.4)	81.1 ± 34.66 (31.3)	58.36 ± 20.22 (50.0)	78.1 ± 30.7 (32.1)
R _{tot}	(kPa*s/L) (% abnormal)	0.2 ± 0.08 (14.3)	0.16 ± 0.07 (3.1)	0.19 ± 0.12 (10.0)	0.17 ± 0.08 (7.1)
D _{L,CO}	SR	-0.7 ± 1.27	-1.3 ± 1.22	-1.12 ± 1.28	-1.12 ± 1.25
	%pred. (% abnormal)	91.26 ± 17.23 (35.7)	83.17 ± 15.52 (37.5)	84.78 ± 16.94 (30.0)	85.5 ± 16.3 (35.7)
C _{L,st}	SR	*-1.16 ± 0.69	†-1.19 ± 1.01	-1.17 ± 1.87	‡-1.18 ± 1.14
	%pred. (% abnormal)	*80.87 ± 12.23 (25.0)	†80.1 ± 18.16 (35.5)	80.29 ± 34.39 (40.0)	‡80.3 ± 20.7 (34.0)
PC ₂₀ H	(mg/mL) (% positive tests)	§6.57 ± 5.25 (57.1)	¶6.15 ± 6.84 (68.8)	**3.14 ± 2.53 (90.0)	††5.7 ± 5.9 (71.4)

*n=12, †n=31, ‡n=53, §n=11, ¶n=27, **n=9, ††n=47

Airway function is usually well preserved in interstitial lung diseases, but not in sarcoidosis (3, 6-13). However, a reduced FEV₁/VC ratio occurred in only 12.5% patients, rates increasing in more advanced stages of the disease. Airflow limitation expressed as lowered MMEF was found in one third of all patients, reaching 50% in stage III. These rates are lower than in formerly studies but close to most recently published (1, 3). The reason may be that in the majority of our patients the duration of the disease was relatively short, while the occurrence of airway obstruction in sarcoidosis seems to be related to disease duration and presence of advanced lung fibrosis (18, 41). None of our patients had stage IV of disease recognized (with the lung fibrosis). Moreover, patients in stage III had comparable static lung

compliance (lung stiffness indicator) to these in stage II. Divergence of results may also be due to the criteria for functional abnormality; in our study an abnormal FEV₁/FVC (as well as for other indices) was based on a LLN defined by the 5th percentile, not on a fixed ratio frequently used in other studies, which leads to overestimating the prevalence of disease on older adults (42). Finally, differences in the prevalence of airflow limitation in various studies might arise from the use of prediction equations that do not fit the population and different populations (higher prevalence in black race) (12).

Although, several authors showed various rates of the incidence of BHR among sarcoidosis patients, this phenomenon is evident in these patients (8, 20, 23-27). The discordant results could be caused by

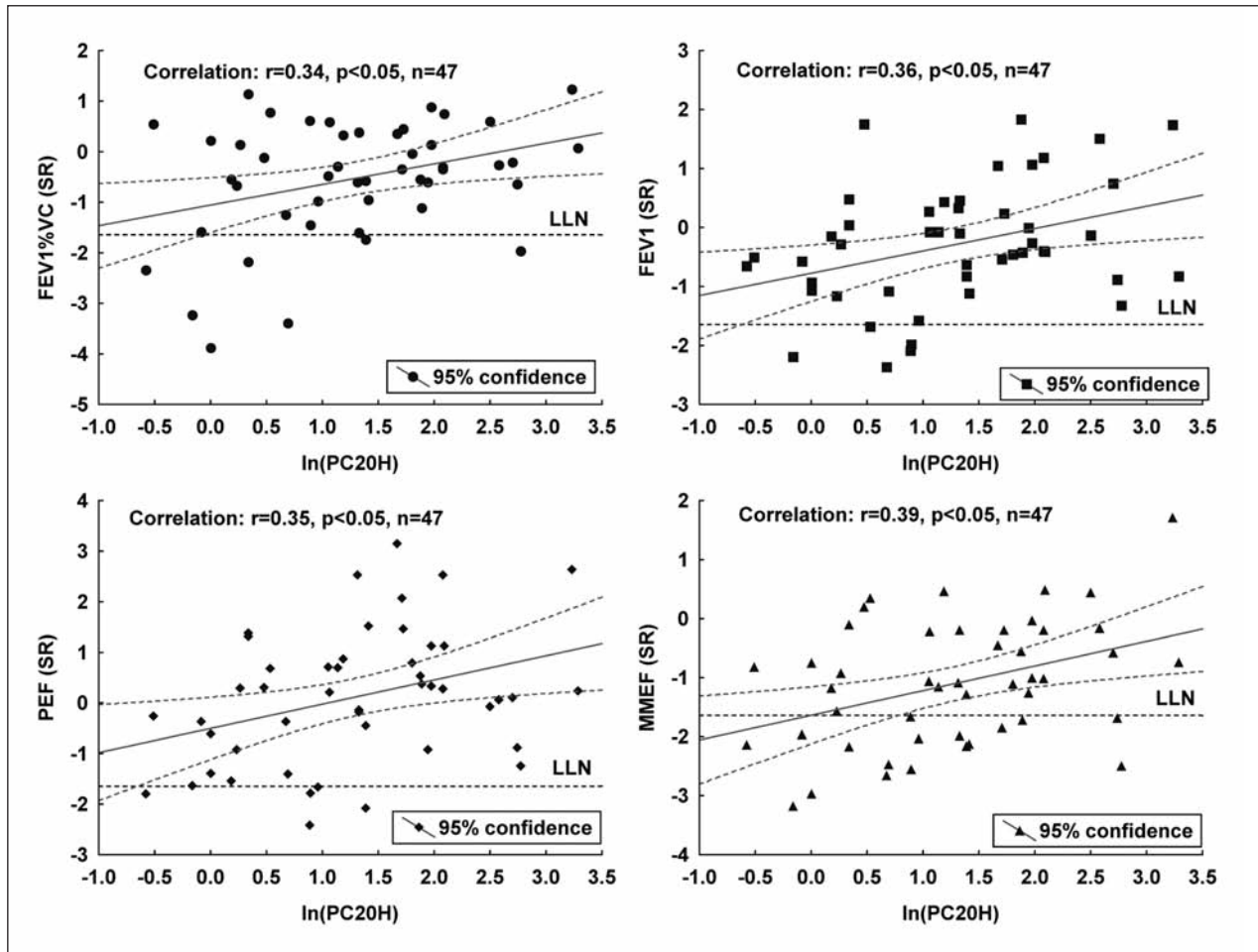


Fig. 1. Spirometric airflow indices in relation to bronchial hyperreactivity expressed as the logarithm of PC20H ($n=47$)

differences in methods used, different criteria for BHR or lack of homogeneity among cases (corticosteroid treatment, presence of atopy, asthma in history). According to ERS guidelines BHR was present in 70% of our patients (32). The number of patients in our group was one of the higher comparing with those described in the past. To avoid known factors influencing BHR we excluded patients with previously diagnosed asthma (also with the history of atopy) and treated with corticosteroids (systemic and topical) 6 months before study. In majority, our patients were current nonsmokers ($n=49$, 87.5%), however 16 of them were ex-smokers. We also included 7 current smokers, so 23 patients were ever-smokers with not to high exposition to tobacco smoke of 7.0 ± 5.4 pack-years. It was decided not to exclude from

the analysis of this subgroup, as the ANOVA tests revealed no relation between BHR results and smoking status (including ever-never smokers as categorical predictor and packyears as continuous predictor), however authors are aware, that it does not mean negative association between them. This decision was supported by data from another study from our centre indicating that smoking has limited (if any) influence on lung function in sarcoidosis (3).

We used a standardized protocol recommended for clinical and epidemiological studies (32). The distribution of the BHR results seems to be close to normal with the maximum about 4 mg/mL of histamine. The percentage of hyperreactive patients is one of the higher reported in the literature dealing with this subject (8, 23-30). It is also much higher

Table 2. Airflow indices (presented as SR, % pred., and percentage of abnormal results), duration of the disease, smoking habit and serum ACE in sarcoidosis patients with and without BHR

Sarcoid patients:		BHR positive (PC ₂₀ H ₂ ≤ 8 mg/mL)	BHR negative (PC ₂₀ H ₂ > 8 mg/mL)	p level (t-test)
n (% of all):		39 (69.6%)	17 (30.4%)	
Active smokers (ex-smokers)		5 (10)	2 (6)	
Exposition (pack-years)		8.2 ± 5.7	4.6 ± 4.0	0.13
time of the disease (years):		4.4 ± 6.4	1.6 ± 2.7	0.08
FEV ₁ %VC	SR	-0.63 ± 1.19	0.06 ± 0.98	0.04
	%pred.	94.6 ± 10.0	100.3 ± 8.5	0.05
	(% abnormal)	(15.4)	(5.9)	
FEV ₁	SR	-0.36 ± 1.01	0.41 ± 1.19	0.02
	%pred.	95.2 ± 13.2	104.6 ± 14.4	0.02
	(% abnormal)	(12.8)	(0)	
MMEF	SR	-1.25 ± 0.95	-0.05 ± 1.73	0.001
	%pred.	70.0 ± 22.4	96.6 ± 39.0	0.002
	(% abnormal)	(38.5)	(17.7)	
PEF	SR	0.08 ± 1.37	0.57 ± 1.56	0.24
	%pred.	101.2 ± 18.7	106.5 ± 19.6	0.33
	(% abnormal)	(12.8)	(5.9)	
MEF ₇₅	SR	-0.29 ± 1.11	0.56 ± 1.36	0.02
	%pred.	93.7 ± 24.9	110.6 ± 28.6	0.03
	(% of abnormal)	(12.8)	(0)	
MEF ₅₀	SR	-0.98 ± 0.94	-0.09 ± 1.52	0.01
	%pred.	74.1 ± 24.6	95.8 ± 38.3	0.01
	(% abnormal)	(28.2)	(11.8)	
MEF ₂₅	SR	-1.30 ± 0.56	-0.48 ± 1.15	0.001
	%pred.	52.3 ± 19.6	81.3 ± 39.6	0.001
	(% abnormal)	(25.6)	(5.9)	
R _{or}	(kPa*s/L)	0.18 ± 0.09	0.16 ± 0.07	0.36
	(% abnormal)	(7.7)	(5.9)	
Serum ACE activity*	(IU/L)	84.4 ± 55.6	75.0 ± 38.5	0.53
	(% abnormal)	(69.2)	(64.7)	

* normal range: 8-52 IU/L

than it was ever noted in a normal healthy population (43). Shorr *et al.* reported one of lowest rates of BHR in sarcoidosis (21.4%), but their patients were newly diagnosed with shorter time of the disease (2/3 of group in stage I, only 5% in stage III), and all were nonsmoking, however all patients in stage III and 1/3 of those in stage II had diagnosed BHR²⁷. Another data with also low incidence of BHR (26%) was presented by Marcias *et al.* (24). It is worth to point out, that 17 of 30 their patients were treated with corticosteroids at the time of investigation, what is well known factor reducing BHR and additionally majority (17/29) were asymptomatic. Similarly in Bechtel *et al.* study 40% patients were treat-

ed⁸. One of the reasons for higher than in previous data percentage of BHR in our patients could be due to that none of our patients was treated using corticosteroids during 6 months before study (however 10 were ever treated due to progressing disease in the past, 9 months to 4 years was the time after stopping treatment to challenge test). The second reason could be that patients with previously diagnosed sarcoidosis were seen in the hospital or outpatients clinic because of more pronounced symptoms and probably increased activity of the disease (2/3 of our patients had elevated serum ACE activity), which would be in agreement with data presented by Shorr *et al.* (27). On the other hand, we did not find a

quantitative correlation between the results of ACE and BHR.

We found a weak but statistically significant correlation between $\ln(PC_{20}H)$ and dynamic airflow limitation indices. These correlations were observed despite the fact that the majority of patients had airflow indices within the normal range. We found also statistically significant differences between the BHR positive and negative patients (table 2). The fact of relationship between initial functional status of airways and BHR is well known especially in COPD patients (44).

Wilsher *et al.* speculated that granulomatous involvement of small baseline diameter of the involved small airways, can potentially increase airway resistance and lead to a false positive bronchoprovocation test (45). The same authors did not find any difference of the exhaled NO, between normal subjects and sarcoidosis patient; therefore this speculation seems more accurate by taking into account the NO test, which was not performed in our patients. In previously published works the relations of BHR with basic obstruction of the large airways were also indicated (8, 23, 26, 29, 46). Our data in this subject are similar to those presented by Marcias *et al.*, because in majority of patients FEV_1 and FEV_1/VC index were in normal range suggesting no signs of obstruction in central airways, while MMEF and MEFs at low and medium lung volumes were quite frequently reduced (24). It is still remaining the question what comes first: BHR? or airway obstruction?

In conclusion: Airway involvement in the course of sarcoidosis is frequently seen (morphological and functional). There is a possibility, that BHR may be a form of manifestation of this involvement. There is a need for studies on mechanisms leading to BHR in this disease. The results of our study confirm the relationships between airflow indices and BHR. The frequency of BHR in sarcoidosis patients is higher than in the normal population and should be considered especially in patients with airflow limitation.

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