Conference Paper

EXERCISE AND ALLERGIC DISEASES

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The aim of this study was to compare exercise-induced bronchial reaction between healthy control subjects and subjects with allergic rhinitis (AR) and allergic asthma (AA). It included 16 controls, 16 subjects with AR and 19 subjects with AA. A skin prick test, pulmonary function test, histamine challenge test and exercise challenge test (ECT) were performed in all subjects. Bronchial reaction to exercise was expressed as the fall index FEV_1 (%), AUC_{0-30} (min x %), and fall index FEF_{25-75} (%).

After ECT, subjects with AA had a significantly greater bronchial reaction to exercise than subjects with AR and controls (respective fall index FEV_1 8.4, 2.9, and 2.4 %, $P=0.0083$; AUC_{0-30} 127.7, 29.6, and 33.1 min x %, $P=0.025$; and fall index FEF_{25-75} 14.6, 0.06, and 1.9 %, $P<0.001$). No difference was found between subjects with AR and controls.

In conclusion, ECT induced a significantly greater bronchial reaction in patients with AA and bronchial hyperreactivity to histamine than in patients with AR and bronchial normoreactivity to histamine and controls. This difference was not found between subjects with AR and controls.

KEY WORDS: *allergic asthma, allergic rhinitis, bronchial reactivity, exercise-induced asthma, exercise test, respiratory function test*

Physical exercise is often seen as a kind of panacea; it has positive physiologic and psychologic effects on individual. However, exercise is also nonpharmacological, nonimmunological, nonspecific stimulus which can induce airway narrowing in the majority of patients with asthma, and this phenomenon is called exercise-induced bronchoconstriction (EIB) (1). Reports on the prevalence of EIB in asthmatic children and adults have ranged between 40 % and 95 % (2-5). Only a few studies have investigated bronchial reaction to exercise in rhinitic subjects, and the occurence of EIB in this population is controversial. Several authors have not found EIB in subjects with allergic rhinitis (6, 7), while others have established EIB in rhinitic subjects with the prevalence of 12-47 % (8, 9). The purpose of this study was to compare bronchial reaction to exercise between subjects with allergic asthma, subjects with allergic rhinitis and healthy controls.

SUBJECTS AND METHODS

Subjects

The study included 16 healthy controls (17-51 years), 16 subjects with allergic rhinitis (AR) (15-45 years) and 19 subjects with allergic asthma (AA) (15-48 years). The healthy controls reported no symptoms of allergic rhinitis and asthma, had a negative skin prick test (SPT) and expressed bronchial normoreactivity to a histamine challenge test. The AR subjects met the EAACI's definition of allergic rhinitis; they reported rhinitic symptoms and had a positive SPT to at least one inhalatory allergen (10). They also expressed bronchial normoreactivity to a histamine challenge test. The AA subjects met the GINA's definition of asthma; they reported asthmatic symptoms and/or have been taking asthma medications and expressed bronchial hyperreactivity to a histamine challenge test (11). They also met the EAACI's definition of

allergic asthma; they had positive SPT to at least one inhalatory allergen.

This study did not include subjects in whom exercise challenge test (ECT) or histamine challenge test were contraindicated (12, 13), nor did it include subjects with upper respiratory viral infections within 3 weeks before the beginning of this study. All subjects on medications for asthma/allergy which can influence on the results of SPT, histamine challenge test or ECT refrained from taking these medications prior to the study: bronchodilators (β2-adrenergic agents 12-48 hours, ipratropium bromide 24 hours, theophyllines 72 hours), antihistamines (4 days prior to the study), coffeine (on the study day) (14). None of the subjects was taking sodium cromoglycate or nedocromil. They continued using inhaled or oral corticosteroids. In subjects with seasonal allergic rhinitis and/or astma, the study was performed out of the pollen season. No attempt was made to pre-select subjects on the basis of their response to exercise.

All participants gave their informed consent before entering the study. This study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki of the World Health Organization in Edinburgh in 2000.

Skin prick test

Trained staff carried out the SPT using a standard procedure (15) with commercial extracts of 15 common inhalatory allergens: grass pollen, Betula ver, Corylus avel, duck feather, Ambrosia elat, Artemisia vulg, Dermatophagoides pter, Cladosporium herb, Alternaria alt, Dermatophagoides far, cat fur, dog fur, Blatella germ, Lepidoglyphus dest, Tyrophagus putr. (ALK-Abello, Denmark) and histamine hydrochloride (1 mg/mL) and buffer solution as controls of positive and negative skin reaction. A 3 mm mean wheal diameter or larger than the negative control was considered positive (16).

Pulmonary function tests

Maximal expiratory flow-volume curve (MEFV curve) was measured in each subject with the standardised method (17) using a Flowscreen (Jaeger, Germany). The best curve was chosen according to the criterion set by the American Thoracic Society (ATS) (18). The curve was used to determine the forced expiratory volume in one second (FEV_1), forced expiratory flow at 50 % of FVC (FEF_{50}), forced expiratory flow at 25 % of FVC (FEF_{25}), forced expiratory flow between 25 and 75 % FVC (FEF_{25-75}). These parameters were expressed as percentage of predicted values (%pred) according to the CECA II norms (Communauté Europeene du Charbon et de l'Acier) (19).

Histamine challenge test

Nonspecific bronchial reaction to histamine was measured using a standardised cumulative dosimeter method according to Chai (20). Test results were expressed as the concentration of histamine (mg/mL) causing a 20 % fall in FEV_1 from the value after inhalation of saline ($PC_{20}FEV_1$). $PC_{20}FEV_1 < 8$ mg/mL was considered as bronchial hyperreaction (12).

Exercise challenge test

The exercise challenge test (ECT) was performed on an electric treadmill (Trackmaster model 400 AC, Patex International, USA) according to the ATS guidelines (13). Each subject went through a standard constant submaximal exercise test. The speed and the slope were adjusted to maintain the heart rate of 85 % of their predicted maximum (calculated as $HR_{max} = 220$ minus the subject's age) (21) for six minutes after two minutes of warming up at a lower heart rate. Heart rate and electrocardiogram were recorded continuously (Archimed ECG, ESAOTE Biomedica, Italy). Blood pressure was recorded every two minutes during ECT and 10 minutes after ECT (Tango, Suntech Medical Instruments, USA). The temperature ranged between 18-28 °C, (mean 24.10±3.00 °C), and humidity ranged between 40 and 85 % (mean 62.35±14.30 %). The MEFV curve was recorded immediately before, immediately after and 3, 5, 7, 10, 15, 20 and 30 minutes after the exercise (22, 13).

Bronchial reaction to exercise was measured by FEV_1 and FEF_{25-75}. FEV_1 was expressed as fall index FEV_1 [fall index FEV_1 = 100 % x (pre-exercise FEV_1 - lowest post-exercise FEV_1)/pre-exercise FEV_1] (12) and as AUC_{0-30} (AUC_{0-30} = Area Under the time-response Curve during 30 min after exercise determined with all fall indices FEV_1 from the baseline value during the 30 min after exercise) (23). FEF_{25-75} was expressed as fall index FEF_{25-75} [fall index FEF_{25-75} = 100% x (pre-exercise FEF_{25-75} – lowest post-exercise FEF_{25-75})/pre-exercise FEF_{25-75}] (24). EIB was defined as fall index $FEV_1 \geq 10$ % (12).

Study design

The subjects visited the Occupational Health and Environmental Medicine Unit of the Institute of Medical

Research and Occupational Health in Zagreb on two consecutive days between 8:00 and 11:30 AM, each day at the same time to avoid diurnal variation in the lung function (25). On the first day, the subjects answered a standardised questionnaire on the history of respiratory and allergic diseases and underwent physical examination, SPT, baseline MEFV curve and histamine challenge test. On the second day, they took the ECT.

Statistical analysis

The statistical analysis was performed using statistical software package STATISTICA (WINDOWS 5.0 A) on an IBM-compatible personal computer. The analysis included the test of proportions with Bonferonni correction, chi-square test, histograms and Kolmogorov-Smirnov one-way test for testing the normality of distributions, Levene's test for testing the homogeneity of variances, Box-Cox transformation for achieving the homogeneity of variances, and one-way analysis of variance (ANOVA) for comparing pre-exercise and post-exercise pulmonary function parameters in the three groups of patients. When ANOVA showed significant differences, post hoc LSD test was peformed for multiple comparisons (controls vs. AR, controls vs AA, AR vs AA). Statistical significance was assumed at $P<0.05$.

RESULTS

Table 1 shows the characteristics of subjects in regard to age, smoking habit, family history of allergy and asthma and history of EIB. The prevalence of family allergies is significantly lower in healthy controls than in AR subjects (6 % v. 67 %, respectively; $P=0.0036$) and AA subjects (6 % v. 50 %, respectively; $P=0.023$). The prevalence of family asthma is significantly higher in AA subjects than in healthy controls (42 % v. 0 %, respectively; $P=0.018$), but there was no significant

Table 1 *Subjects' characteristics. Smoking index = years of smoking x number of cigarette per day, P=statistical significance: $P^A<0.05$ (proportion test with Bonferonni correction), $P^B<0.05$ (analysis of variance / ANOVA), $P^C<0.05$ (χ^2 test), $P^D<0.05$ (Kruskal Wallis ANOVA)*

GROUP	AGE		SMOKING			POSITIVE HYSTORY		
	$\bar{X}$ ± SD	Range	N (%)	Smoking index. Median	Range	Allergy in family N (%)	Asthma in family N (%)	Asthma in exercise N (%)
Controls N=16	30,19 ± 9,59	17-51	4 (25)	240	60-450	1 (6)	0 (0)	0 (0)
Allergic rhinitis N=16	26,69 ± 8,93	15-45	4 (25)	134	6-400	11 (67)	5 (31)	0 (0)
Allergic asthma N=19	27,16 ± 9,46	15-48	3 (16)	20	4-100	9 (50)	8 (42)	12 (63)
P	$P^B=0,59$		$P^C=0,84$		$P^D=0,25$			

$P^A=0,0036$; $P^A=0,066$; $P^A=1$; $P^A=0,023$; $P^A=0,018$; $P^A=0,0012$; $P^A=0,032$; $P^A=0,51$; $P^A=0,0012$

Table 2 *Pulmonary function at rest by the groups. FEV_1=forced expiratory volume in one second; FEF_{25-75}=forced expiratory flow between 25 and 75% forced vital capacity (FVC); FEF_{50}=forced expiratory flow at 50% of forced vital capacity (FVC), FEF_{25}= forced expiratory flow at 25% of forced vital capacity (FVC), %, pred=percent of predicted values (CECA II), P=statistical significance: $P^A<0.05$ (analysis of variance/ANOVA), $P^B<0.05$ (post-hoc LSD test)*

GROUP	FEV_1 (%pred)			FEF_{25-75} (%pred)			FEF_{50} (%pred)			FEF_{25} (%pred)		
	$\bar{X}$ %	SD	P^B	$\bar{X}$ %	SD	P^B	$\bar{X}$ %	SD	P^B	$\bar{X}$ %	SD	P^B
Controls N=16	111,3	13,9		96,4	23,2		98,1	22,2		91,5	30,3	
			0,82			0,38			0,49			0,72
Allergic rhinitis N=16	112,7	18,4		104,3	25,8		104,8	29,9		95,3	35,7	
			0,0020			<0,001			<0,001			<0,001
Allergic asthma N=19	93,6	18,9		60,2	26,8		62,6	27,9		53,9	23,7	
			0,0040			<0,001			<0,001			<0,001
P^A	0,025 (F=6,8; df = 2)			<0,001 (F=15,3; df = 2)			<0,001 (F=12,6; df = 2)			<0,001 (F=10,4; df = 2)		

difference between healthy controls and AR subjects (0 % v. 31 %, respectively; P=0.066) and between AR and AA subjects (31 % v. 42 %, respectively; P=0.51). The History of EIB was positive only in AA subjects (12/19=63 %).

Pulmonary function parameters FEV_1, FEF_{25-75}, FEF_{50} i FEF_{25} were measured before ECT, expressed as the percent of predicted values (%pred) (CECA II), and evaluated as mean values in every group (Table 2). Subjects with allergic asthma had significantly lower pulmonary function parameters than AR subjects and healthy controls: FEV_1%pred (P=0.0025), FEF_{25-75}%pred (P<0.001), FEF_{50}%pred (P<0.001) and FEF_{25}%pred (P<0.001).

Bronchial reaction after ECT was evaluated as fall index FEV_1, AUC_{0-30} and fall index FEF_{25-75} expressed as mean values in every group. Additionally, fall index FEV_1 was expressed as individual values after ECT. After ECT, AA subjects had a significantly higher fall index FEV_1 than AR subjects (8.4 v. 2.9, respectively; P=0.015) and healthy controls (8.4 v. 2.4, resepectively; P=0.0044). No difference was found between AR subjects and controls (Figure 1). All healthy subjects and all AR subjects had fall index FEV_1<10 %. In the group of AA subjects, fourteen had fall index FEV_1<10 %, and five had FEV_1≥10 % (Figure 2). After ECT, AA subjects had a significantly higher AUC_{0-30} than AR subjects (127.7 v. 29.6, respectively; P=0.018) and healthy controls

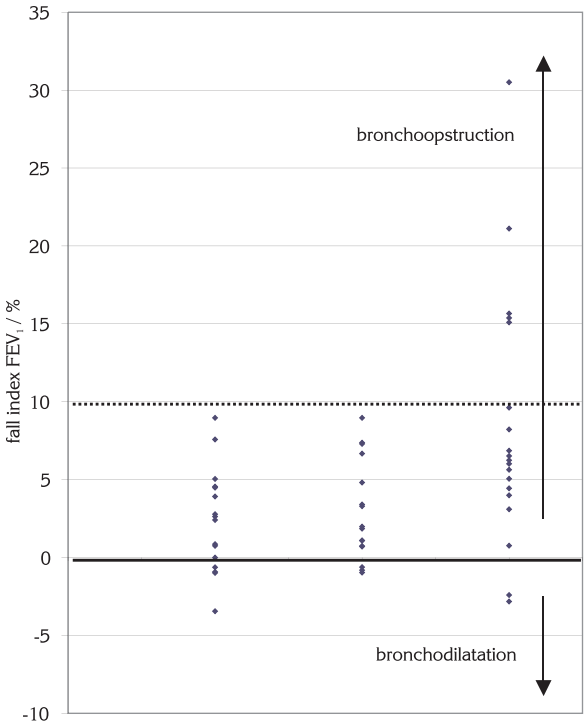

Figure 2 *Individual fall index FEV_1(% of FEV_1 at rest) after exercise challenge test. Fall index FEV_1 = 100 % x (pre-exercise FEV_1 – lowest post-exercise FEV_1) / pre-exercise FEV_1. FEV_1=forced expiratory volume in one second; C=controls, AR=allergic rhinitis, AA=allergic asthma, ... threshold for significant fall index FEV_1.*
All healthy subjects and all AR subjects had fall index FEV_1<10 %. Fourteen AA subjects had fall index FEV_1<10 % and five had FEV_1≥10 %.

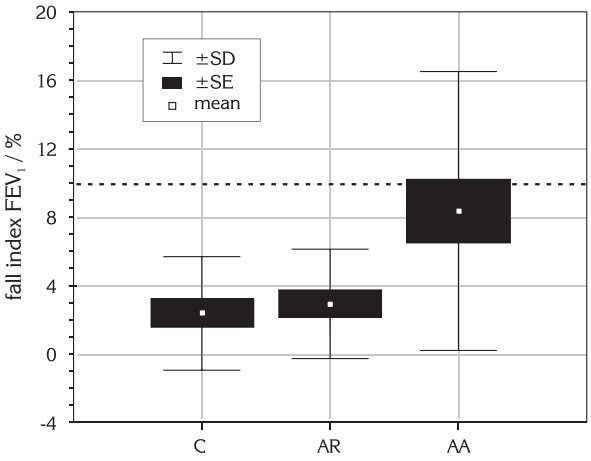

Figure 1 *Fall index FEV_1 (% of FEV_1 at rest) after exercise challenge test (ECT). Fall index FEV_1 = 100% x (pre-exercise FEV_1 – lowest post-exercise FEV_1) / pre-exercise FEV_1. FEV_1=forced expiratory volume in one second; C=controls, AR=allergic rhinitis, AA=allergic asthma, ... threshold for significant fall index FEV_1; statistical significance: P<0.05 (post-hoc LSD test)*
After ECT, AA subjects had a significantly higher fall index FEV_1 than the other two groups. No difference was found between AR and control subjects. (AA v. AR = 8.4 v. 2.9 %, P=0.015; AA v. Z = 8.4 v. 2.4 %, P=0.0044; AR v. Z = 2.9 v. 2.4 %, P=0.65)

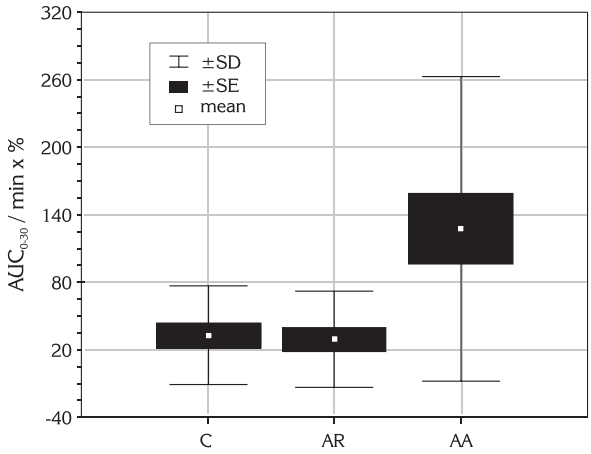

Figure 3 *AUC_{0-30} (min x %) after exercise challenge test (ECT). AUC_{0-30}=Area Under the time-response Curve during 0-30 min. after exercise, C=controls, AR=allergic rhinitis, AA=allergic asthma; statistical significance: P<0.05 (post-hoc LSD test)*
After ECT, AA subjects had a significantly higher AUC_{0-30} than the other two groups. No difference was found between AR and control subjects. (AA v. AR = 127.7 v. 29.61 %, P=0.018; AA v. Z = 127.7 v. 33.1 %, P=0.022; AR v. Z = 29.6 v. 33.1 %, P=0.93)

(127.7 v. 33.2, respectively; P=0.022). No difference was found between AR and control subjects (Figure 3). After ECT, AA subjects had a significantly higher fall index FEF_{25-75} than AR subjects (14.6 v. 0.06, respectively; P<0.001) and healthy controls (14.6 v. 1.9, respectively; P<0.001). No difference was found between AR and control subjects (Figure 4).

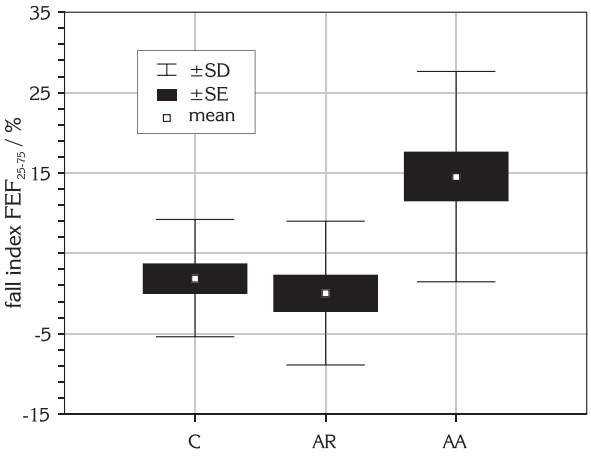

Figure 4 *Fall index FEF_{25-75} (% FEF_{25-75} at rest) after exercise challenge test (ECT) . Fall index FEF_{25-75} (%) = 100 % x (pre-exercise FEF_{25-75} – lowest post-exercise FEF_{25-75}) / pre-exercise FEF_{25-75}.FEF_{25-75}=forced expiratory flow between 25 and 75 % forced vital capacity; C=controls, AR=allergic rhinitis, AA=allergic asthma; statistical significance: P<0.05 (post-hoc LSD test) After ECT, AA subjects had a significantly higher fall index FEF_{25-75} than the other two groups. No difference was found between AR and control subjects. (AA v. AR = 14.6 v. 0.06 %, P<0.001; AA v. Z = 14.6 v. 1.9 %, P<0.001; AR v. Z = 0.06 v. 1.9 %, P=0.61)*

DISCUSSION

Allergic rhinitis is a symptomatic disorder resulting from an immunological hypersensitive reaction in the nose (10). The understanding of the pathogenesis of allergic rhinitis and allergic asthma has changed over the last ten years; earlier they were considered two different diseases and now they are considered manifestations of the same disease entity under the concept of a "uniform airway disease" (26). Patients with a mild disease express only symptoms of rhinitis, while patients with a severe disease express both rhinitis and asthma (27). The ARIA initiative (Allergic Rhinitis and its Impact on Asthma) started in collaboration with the WHO (28). Many investigations about bronchial reactivity in rhinitic patients established that 28-40 % of AR patients have bronchial hyperreactivity to histamine or metacholine, which is the main feature of asthma (29-31). However, only a few studies have investigated bronchial reactivity to exercise in AR patients, and results are controversial.

Exercise-induced bronchoconstriction is frequent in asthmatic children and adults, with the prevalence between 40 % and 95 % (2-5). So wide a range results from differences between the studies which include differences in the intensity of the exercise, variations in the definition of EIB, differences in the methods used to detect the response, difference in the stage of disease between the subjects and the failure to standardize the environmental variables that control the magnitude of the obstruction. The European Respiratory Society (ERS) and the American Thoracic Society (ATS) published guidelines for ECT (13, 22). However, only a few studies observed these guidelines. It is generally accepted that bronchial reaction to exercise is measured with fall index FEV_1. According to the ERS and ATS guidelines, fall index $FEV_1 \geq 10$ % is considered as positive bronchial reaction, because it is beyond two standard deviations of the mean change FEV_1 in healthy control after ECT (22). For the last ten years, some authors have been expressing bronchial reaction to exercise as AUC_{0-30}, which summarizes both the extent and the duration of bronchoconstriction after exercise (23, 32). Fall index FEF_{25-75} is used in order to detect bronchial reaction to exercise in small airways.

The results of our study showed a significantly greater bronchial reaction to exercise in AA subjects than in AR subjects and healthy controls. There was no difference in bronchial reaction to exercise between AR subjects and healthy controls. All available studies established a significantly higher bronchial reaction to exercise in asthmatic subjects than in AR subjects and healthy controls (5-8, 33, 34). Just like in our investigation, several authors (7, 35, 36) found no difference between AR subjects and healthy controls. However, other authors found a significantly greater bronchial reaction to exercise (greater fall index FEV_1, fall index FEF_{25-75} and/or fall in PEFR) in AR subjects than in healthy controls (5, 33, 34). As we interpreted the fall index of $FEV_1 \geq 10$ % as positive bronchial reaction to exercise, we found EIB in 33 % of asthmatics. None of the AR subjects and healthy controls responded positively, which is in accordance with some other studies (6, 7). In contrast, several other authors found EIB in AR subjects (5, 8, 9, 33, 34).

Our results are not completely comparable with other studies for two reasons: 1) different definition of groups, 2) different methods of evaluation of bronchial reaction to exercise. Most of the studies which have found EIB in AR patients had their asthma diagnosis

based solely on the questionnaire (33), history (5, 8) or history with physical examination (9). Anderson Nish (37) found that as many as 50 % of asthmatic subjects were not aware of their asthma diagnosis. EIB was particularly common in these undiagnosed asthmatics. In studies that found EIB in nonasthmatic subjects, it may be that the subjects with EIB have been misclassified as nonasthmatic. Although they did not report any respiratory symptoms at enrolment, they might have had mild symptoms not recognised as bronchial asthma. To avoid this misclassification our study included the history, physical examination, SPT, registration of MEFV-curve at rest and histamine challenge test for every subject. Subjects with allergic rhinitis met the definition of allergic rhinitis according to EAACI, and none of the rhinitics showed bronchial hyperreaction to histamine. Subjects with allergic asthma met the definition of asthma according to GINA and the definition of allergic asthma according to EAACI.

When we considered other methods for the evaluation of bronchial reaction to exercise, we decided not to measure PEFR with Mini-Wright peak flow meter, as it could give many false positive results (38). In the case of central airway obstruction (vocal cord dysfunction, abnormal posterior motion of arytenoid region, or tracheal narrowing), a person can have a positive history of EIB and positive bronchial reaction to exercise measured with PEFR (39). These rare cases can be distinguished from exercise-induced bronchoconstriction by examining the full inspiratory and expiratory flow-volume curve (13). Some investigations which have found EIB in rhinitic patients evaluated bronchial reaction to exercise by measuring PEFR with Mini-Wright peak flow meter (9, 33) and they did not make serial registration of the flow-volume curve according to the ERS and ATS guidelines. It is possible that AR patients and positive EIB patients in those studies had an unrecognised central airway obstruction. In this investigation, ECT was performed according to the ERS and ATS guidelines with serial registration of MEFV-curve.

The limitation of this study is a relatively smaller number of subjects compared with some other studies. This could have certain implication on the results obtained and their interpretation.

CONCLUSION

Unlike in allergic asthma, bronchial reactivity to exercise is still seldom investigated in allergic rhinitis. Only since the adoption of the idea that rhinitis and asthma are the manifestations of the same disease have the two been expected to show similar features.

In our study, bronchial reaction to exercise significantly differed between AR patients with bronchial normoreactivity to histamine and AA patients with bronchial hyperreactivity to histamine. The bronchial reaction to exercise did not differ between AR patients and nonallergic asymptomatic persons, both with bronchial normoreactivity to histamine. Our results suggest that bronchial reactivity to histamine in allergic patients influences bronchial reactivity to exercise. The relationship between bronchial reactivity to exercise and natural course of respiratory allergic diseases needs further investigation.

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Sažetak

TJELESNO OPTEREĆENJE I ALERGIJSKA ASTMA

Malo je istraživanja ispitivalo bronhalnu reakciju na tjelesno opterećenje u oboljelih od alergijskog rinitisa. Cilj ovog istraživanja bio je ispitati bronhalnu reakciju na tjelesno opterećenje u oboljelih od alergijske astme, alergijskog rinitisa i zdravih ispitanika.

U ispitivanje je uključeno 16 zdravih ispitanika dobrovoljaca (17-51 godina), 16 ispitanika oboljelih od alergijskog rinitisa prema kriterijima EAACI (15-45 godina) i 19 oboljelih od alergijske astme prema kriterijima GINA-e (15-48 godina). U svih ispitanika napravljeno je kožno prick testiranje, određena je ventilacijska funkcija pluća registracijom MEFV-krivulje, napravljen je provokativni bronhalni test histaminom i konstantni submaksimalni test tjelesnim opterećenjem. Bronhalna reakcija na tjelesno opterećenje evaluirana je kao indeksni pad FEV_1, AUC_{0-30} i indeksni pad $FEF_{25-75.}$

Nakon tjelesnog opterećenja oboljeli od alergijske astme u odnosu na oboljele od alergijskog rinitisa i zdrave ispitanike imali su značajno veći indeksni pad FEV_1 (8,4, 2,9, 2,4 %; P=0,0083), značajno veću AUC_{0-30} (127,7, 29,6, 33,1 min x %; P=0,025), kao i značajno veći indeksni pad FEF_{25-75} (14,6, 0,06, 1,9 %; P<0,001). Nije utvrđena razlika u veličini bronhalne reakcije između oboljelih od alergijskog rinitisa i zdravih. EIB na osnovi indeksnog pada $FEV_1 \geq 10$ % utvrđen je samo u oboljelih od alergijske astme (33 %).

Konstantno tjelesno opterećenje induciralo je značajno veću bronhalnu reakciju u oboljelih od alergijske astme nego u oboljelih od alergijskog rinitisa i zdravih, što nije utvrđeno između rinitičara i zdravih ispitanika.

KLJUČNE RIJEČI: *alergijska astma, alergijski rinitis, bronhalna reaktivnost, bronhospazam induciran tjelesnim opterećenjem, test tjelesnim opterećenjem, testovi ventilacijske funkcije pluća*

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