Katarzyna Hildebrand, Tadeusz Przybyłowski, Marta Maskey-Warzęchowska, Ryszarda Chazan

Department of Internal Diseases, Pulmonology and Allergology of the Medical University of Warsaw
Head: Prof. R. Chazan

Usefulness of selected tests in the diagnosis of exercise-induced bronchoconstriction

Przydatność wybranych testów w rozpoznawaniu powysiłkowego skurczu oskrzeli

Abstract

Introduction: Indirect airway challenge tests are commonly used in the diagnostics of exercise-induced bronchoconstriction (EIB), defined as a post-exercise decrease in $FEV_1 \geq 10\%$. The aim of this study was to evaluate the diagnostic value of bronchial hyperreactivity tests in the diagnosis of EIB.

Material and methods: Forty-two subjects were allocated into 3 groups: A — 19 steroid-naive asthma patients; D — 11 non-asthma patients reporting symptoms suggestive of EIB (dyspnoea, wheezing, and cough provoked by exercise); and K — 12 healthy controls. Subjects filled a questionnaire regarding symptoms related to exercise and underwent: inhaled bronchial challenge to methacholine (Mch), adenosine 5′-monophosphate (AMP), and exercise challenge on a treadmill. With a cut-off of ≥ 10% and ≥ 15% decrease in FEV1, EIB was diagnosed in 47% and 37% of asthma patients, respectively. Exercise-induced bronchoconstriction was found in 27% of subjects in group D and in none of the controls, irrespectively of the FEV_1 criterion.

Results: The analysis of the questionnaire revealed that a single symptom cannot be used to predict EIB. Symptoms occurring after termination of exercise, but not during exercise, characterize EIB more precisely. The analysis showed that the most useful measure to diagnose EIB can be a combination of bronchial challenge to AMP and typical symptoms of exercise-induced bronchoconstriction (i.e. dyspnoea, wheezing, and coughing provoked by exercise) with a sensitivity of 70%, specificity of 94%, PPV of 78%, NPV of 91%, and LR of 11.2.

Conclusions: Symptoms suggestive of EIB do not have acceptable sensitivity and specificity for the diagnosis of exercise-induced bronchoconstriction. The most useful measure to diagnose EIB is the combination of typical symptoms of EIB with a positive challenge to AMP.

Key words: asthma, exercise-induced bronchoconstriction, bronchial challenge tests

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Introduction

Exercise-induced bronchoconstriction (EIB) is a transient bronchoconstriction which occurs during or, more often, after vigorous exercise [1–4]. Some authors distinguish the term of exercise-induced asthma (EIA), which applies to asthmatic patients with symptoms of bronchoconstriction following physical exercise, and limit the diagnosis of exercise-induced bronchospasm (EIB) to patients without other symptoms of asthma [5–7]. According to the 2007 American Academy of Allergy, Asthma, and Immunology Work Group report, the frequency of EIA in the general population varies from 5 to 20% [5] and reaches as much as 90% in patients with asthma. Exercise-induced bronchoconstriction poses a significant problem in athletes. The prevalence of EIB in athletes participating

Address for correspondence: Katarzyna Hildebrand MD, PhD, Department of Internal Diseases, Pulmonology and Allergology of the Medical University of Warsaw, ul. Banacha 1a St., 02–097 Warszawa, tel.: (22) 599 25 62, e-mail: katarzyna.hildebrand@wum.edu.pl

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in the summer Olympics ranges from 10 to 20% and reaches 50–70% in competitive winter sports athletes (especially cross-country skiing and skating) [2, 5].

Typical symptoms reported by patients affected by EIB are: dyspnoea, cough, wheezing, chest tightness, and shortness of breath. Symptoms usually appear several minutes after exercise, although in case of prolonged physical activity of medium-intensity they may also appear during the exertion [5].

In the differential diagnosis of EIB one should consider, above all, chronic diseases of the respiratory tract and cardiovascular system, gastroesophageal reflux, or hyperventilation syndrome. Poor physical fitness or overtraining may also raise suspicion of EIB, especially in patients with high self-expectations [5, 6, 8].

According to the Global Initiative for Asthma (GINA) report, EIB is one of the forms of bronchial hyperreactivity [10]. Exercise is a physical stimulus causing airway constriction through an indirect mechanism, i.e. through activation of inflammatory cells and stimulation of nerve endings that release proinflammatory mediators and cytokines, causing bronchial constriction [11].

Diagnosis of EIB is based on demonstrating a reduction in the forced expiratory volume in 1 second (FEV_1) by at least 10% of the baseline value after physical exercise performed under controlled conditions [1, 5, 13]. Some researchers claim that the criterion of a 15% reduction in FEV_1 is more diagnostic, especially with regard to diagnostic tests conducted in the field or for epidemiological purposes [1, 13].

Basing the diagnosis of EIB solely on the information from a patient's history may lead to both overdiagnosis as well as underdiagnosis of this condition [7, 14]. Due to the cost and poor availability of the instruments that ensure proper conditions during the exercise challenge test, there are attempts being made to use other diagnostic tests such as eucapnic voluntary hyperpnoea (EVH), or bronchial challenge tests using mannitol or non-isotonic aerosols [2, 3, 5, 7]. Some researchers suggest that bronchial challenge test with adenosine monophosphate (AMP) as a stimulus to evoke bronchospasm in a mechanism similar to that of exercise may be useful in diagnosing EIB [3, 5, 11]. No publications presenting such an evaluation in a systematic manner were found in the literature. The lack of such studies may be the reason why bronchial challenge with AMP test has not been yet introduced to the standards of EIB diagnosis in athletes [7].

The aim of this study was to evaluate the usefulness of various hypersensitivity tests as well as a symptom questionnaire in diagnosis of EIB. The study protocol was approved by the Bioethics Committee at the Medical University of Warsaw (document no. KB/58/2004)

Material and methods

Forty-two subjects aged 30 ± 8 years participated in the study (17 women, 25 men). According to a preliminary evaluation, they were allocated into the following groups: A — 19 patients with allergic asthma; D — 11 subjects with symptoms suggestive of EIB but without other symptoms of asthma; and K — 12 healthy volunteers who served as a control group. Group characteristics are presented in Table 1. Subjects were recruited among patients under the care of a pulmonology outpatient clinic, to which they had been referred due to suspicion of asthma or who had been treated for episodic asthma. None of the participants was treated with glucocorticosteroids (systemic or inhaled) or antileukotriene modifiers during the period of at least 3 months prior to for the study. Until the end of the study, all patients were using a short-acting β-agonist – fenoterol or salbutamol – on as-needed basis.

History-taking and physical examinations were aimed to allocate subjects into appropriate groups and to assess possible contraindications to the tests. A questionnaire on EIB symptoms was conducted in all cases, i.e. occurrence of dyspnoea, coughing, wheezing, chest tightness during and after exercise, and relation between symptoms and the seasons (winter/summer). Total IgE level and peripheral blood eosinophil count were measured and skin tests for most common inhalant allergens were performed to detect atopy.

Spirometry

Spirometry was performed according to the recommendations of the Polish Respiratory Society [12] using a Lungtest 1000 spirometer (MES, Cracow, Poland). Before the challenge tests, the patients were asked to stop inhaled medications, as recommended by the American Thoracic Society (ATS) [13].

Methacholine bronchial challenge test

Bronchial challenge test with methacholine was performed using a Lungtest 1000 spirometer with an ISPA module. Methacholine chloride was used for the study (Prospecta, Poland). Examinations were carried out by applying nebulization for

2 minutes in accordance with the ATS recommendations [13]. The result was considered negative when the PC_{20} (provocative concentration leading to a decrease of FEV_1 > 20% of baseline) exceeded 16 mg/ml.

Adenosine monophosphate challenge test

Bronchial challenge test with AMP was completed using the same instruments as in the methacholine tests. Studies with AMP were carried out by applying nebulization for 2 minutes in accordance with ERS recommendations [11]; adenosine monophosphate sodium salt was used for the tests (Sigma-Aldrich, Poland). Twofold incremental concentrations were used, beginning with 0.39 mg/ml and ending with 400 mg/ml. The test result was considered negative when PC_{20} exceeded 400 mg/ml.

Exercise challenge test

Every subject completed two exercise studies: a cardiopulmonary exercise test assessing maximal exercise capacity of a given patient, and an exercise challenge test conducted according to ATS guidelines [13] — the subject inhaled air of a temperature of 20–25°C and humidity of less than 50% (humidity and temperature of the mixture were constantly monitored with sensors installed in the Douglas bag). Examinations were carried out on a treadmill using a computerized Ergo 2000 system (MES, Poland), which allowed the analysis of ventilatory parameters on a breath-by-breath basis. Work load was guided by patient ventilation – the target value was within the range of 40–60% of maximal ventilation reached during the first test. Heart rate (HR) and oxygen uptake (VO_2) were simultaneously monitored and the load was adapted in a manner to keep these values within respective ranges of 80–90% and about 80% of the values reached in the first test.

Spirometry with recording of the flow-volume loop was done before the exercise challenge test and immediately after it ended, which was approx. at the 2nd minute, and then at the 5th, 10th, 15th, and 20th minutes. There were 5–7 days of interval between the subsequent challenge tests and the order of them was random.

Statistical analysis

Quantitative variables were presented as means ± standard deviations (SD) with the exception of PC_{20} values for methacholine and AMP, which were shown as medians and interquartile ranges. Qualitative variables were presented as the numbers and percentages they comprise in a given data set.

While evaluating the diagnostic values of particular tests, their sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and the likelihood ratios (LR) were assessed. Depending on the distribution of the studied variables and the character of intragroup comparisons, the student's t-test was used for correlated or uncorrelated samples, as well as a Mann-Whitney U or Kruskall-Wallis ANOVA tests. Statistical analysis was performed using Statistica for Windows analysis software (StatSoft, Inc. STATISTICA version 10. www.statsoft.com.). A p value 0.05 was considered significant.

Results

Asthma patients were characterized by a higher eosinophil count in the peripheral blood and a higher total IgE serum concentration in comparison to subjects with exercise-induced dyspnoea or healthy individuals (Table 1). All asthmatic patients had positive skin tests. Mean values of lung function parameters in the studied groups were within normal ranges and no significant differences were observed between groups A, D, and K (Table 1).

The results of methacholine challenge tests were positive in all patients with asthma, in 4 (36%) subjects from group D, and in 5 (42%) from group K. The PC_{20} value in asthmatic patients was significantly lower than that acquired for groups D and K (Table 2). The AMP test was positive in 16 (82%) patients from group A. In groups D and K results of the AMP test were positive in 2 (18%) and 1 (8%) subjects, respectively. The PC_{20} value for AMP in patients with asthma was significantly lower than in other groups (Table 2). In all challenge tests (methacholine, AMP, exercise) the highest percentage of FEV_1 reduction was observed in asthmatic patients (Table 2).

The occurrence of EIB in all groups was assessed in two ways: application of the criterion of FEV_1 reduction following exercise by at least 15% or by 10% of the initial value. Following an exercise challenge, FEV_1 reduction by at least 15% occurred in 7 (37%) patients with asthma. When applying the 10% FEV_1 reduction criterion, the number of patients with diagnosis of EIB rose to 9 (47%). Among subjects complaining of exercise-induced dyspnoea, lowering the cut-off value of post-exercise FEV_1 reduction for EIB diagnosis to 10% did not influence the number of diagnoses — in both cases EIB was diagnosed in 3 (27%) subjects. None of the subjects from the control group was diagnosed with EIB (Figure 1).

In the next step, an analysis was conducted, in which the main independent variable was the

Table 1. Study group characteristics

Parameters	A n = 19	D n = 11	K n = 12
Age (years)	31.2 ± 7.6	29.5 ± 8.8	28.1 ± 8.9
Sex (%)			
K — females			
M — males	K 9 (47) M 10 (53)	K 3 (27) M 8 (73)	K 5 (42) M 7 (58)
BMI [kg/m^2]	24.3 ± 5.2	24.7 ± 3.8	23.8 ± 1.9
Smokers n (%)	3 (16)	2 (18)	1 (8)
Eosinophils in peripheral blood [10^3/μL]	0.31 ± 0.2*	0.19 ± 0.06	0.14 ± 0.1
Eosinophils (%)	3.9 ± 3.1	3.1 ± 1.8	1.8 ± 1.3
Total IgE [U/ml]	170 ± 242*	136 ± 162**	24 ± 19
Positive skin prick tests n (%)	19 (100)*	7 (64)	5 (42)
FEV_1 [l]	3.5 ± 0.6	3.9 ± 0.5	3.9 ± 0.6
FEV_1% predicted	94 ± 12	98 ± 10	101 ± 10
FVC [l]	4.6 ± 0.9	4.8 ± 0.8	4.9 ± 1.0
FVC% predicted	105 ± 14	102 ± 13	107 ± 11
FEV_1%FVC	76 ± 8	82 ± 8	80 ± 6

*Statistically significant difference A v. K
**Statistically significant difference D v. K
A — asthma patients, D — exertional dyspnea patients, K — controls
BM — body mass index; IgE — immunoglobulin E; FEV_1 — forced expiratory volume in 1 second; FVC — forced vital capacity

Table 2. Bronchial challenge to methacholine, AMP and exercise

	A	D	K
PC_{20}Mch [mg/ml]§	0.60 (0.09–1.47)*#	17.0 (0.41–17.0)	17.0 (4.93–17.0)
Δ%FEV_1Mch	24.32 ± 5.13*#	15.0 ± 10.79	15.5 ± 7.69
PC_{20}AMP [mg/ml]§	7.34 (0.55–81.8)*#	401 (401–401)	401 (401–401)
Δ%FEV_1AMP	28.26 ± 15.20*#	11.09 ± 9.96	7.5 ± 7.67
ΔFEV_1max%	11.5 ± 13.5*#	6.6 ± 11.0	0.4 ± 4.4

*Statistically significant difference A v. K
#Statistically significant difference A v. D
§Data are presented as medians (interquartile range). In subjects with methacholine PC_{20}>16 mg/ml its value was arbitrary coded as 17 mg/ml; in patients with AMP PC_{20}> 400 mg/ml its value was coded as 401 mg/ml.
A — asthma patients, D — exertional dyspnea patients, K — controls
FEV_1 — forced expiratory volume in 1 second; Δ%FEV_1Mch — % of FEV_1 decrease during methacholine challenge; Δ%FEV_1AMP — % of FEV_1 decrease during AMP challenge; ΔFEV_1maks% — % of FEV_1 decrease during exercise challenge

diagnosis of EIB. All subjects (n = 42) were divided into 2 subgroups:

- EIB (+) — patients diagnosed with exercise-induced bronchospasm after an exercise test. Reduction of FEV_1 by at least 15% with respect to the predicted value was considered significant for the diagnosis of EIB. This subgroup consisted of 10 subjects: 7 from group A and 3 from group D;
- EIB (–) — patients without bronchospasm after exercise challenge test (n = 32).

This division was performed in order to evaluate the usefulness of selected symptoms and bronchial challenge tests with methacholine and AMP for diagnosis of EIB.

Exercise-induced bronchospasm was diagnosed in 10 (24%) subjects out of the entire group. Both groups differed in terms of numbers and percentages of eosinophils and total IgE concentrations. Lung function parameters were similar in both groups, although EIB (+) patients had significantly lower PC_{20} values for methacholine and for

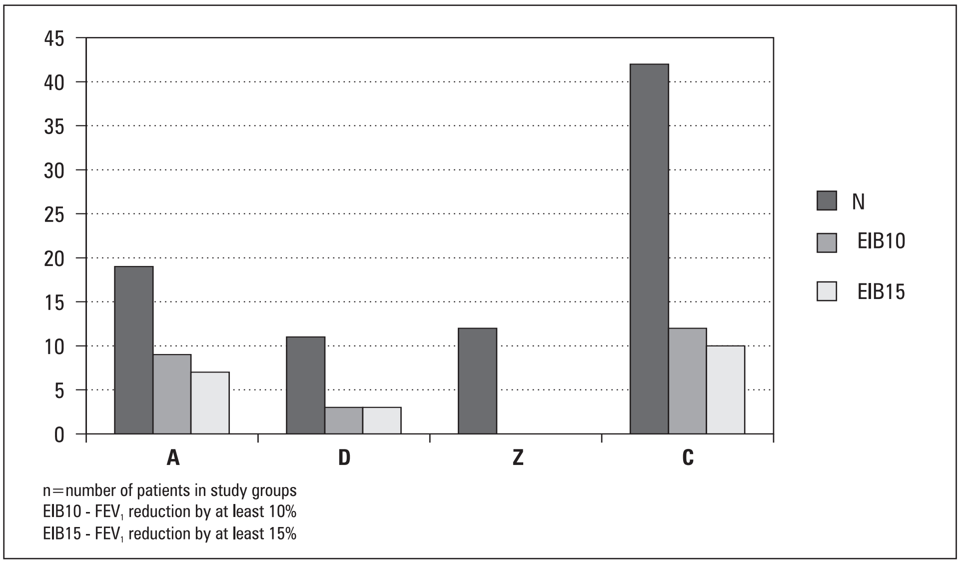

Figure 1. Prevalence of exercise-induced bronchoconstriction in study groups

Table 3. Comparison of EIB(+) and EIB(–) groups

Parameter	EIB(+) n = 10	EIB(–) n = 32	p
Smokers n (%)	1 (10)	5 (16)	NS
Eosinophils [$10^3/\mu l$]	0.38 ± 0.24	0.18 ± 0.13	0.003
Eosinophils (%)	5.2 ± 3.5	2.4 ± 1.5	0.03
Total IgE [U/ml]	250.3 ± 319.9	75.6 ± 94.3	0.01
Skin prick tests (%)	90	67	NS
FEV_1 [l]	3.6 ± 0.8	3.7 ± 0.6	NS
% of predicted	91 ± 11	99 ± 11	NS
FEV_1%FVC	77 ± 9	79 ± 7	NS
PC_{20}Mch [mg/ml]	2.0 ± 5.3	8.4 ± 7.6	0.001
Δ%FEV_1Mch	22.8 ± 6.4	18.3 ± 9.2	NS
PC_{20}AMP [mg/ml]	64.4 ± 135.8	284.8 ± 176.5	< 0.001
Δ%FEV_1AMP	36.3 ± 16.4	12.1 ± 9.4	< 0.001
ΔFEV_1max%	24.8 ± 7.9	1.3 ± 5.7	< 0.001

Abbreviations below the Table 2

AMP (Table 3). Also, significant differences in the severity of bronchospasm were noted during challenge with AMP: in the EIB (+) group, FEV_1 reduction was 36.3 ± 16.4% and 12.1 ± 9.4% in the EIB (–) group ($p < 0.001$). Such a difference was not found in tests with methacholine. After analysing the EIB symptom questionnaire, we selected a group of symptoms most often reported by the patients, i.e. dyspnoea, wheezing, and exercise-induced cough. It was concluded that the symptoms during exertion occurred with the same frequency in both groups, but post-exertion symptoms occurred with a significantly greater frequency in the EIB (+) group. These patients also complained of these symptoms more often during winter months (Table 4).

Exercise-induced bronchoconstriction may be diagnosed (using the ΔFEV_1max% ≥ 15%) with 80% sensitivity and 87% specificity (Table 5) on the grounds of occurrence of the most typical symptoms (dyspnoea, wheezing, exercise-induced cough). Methacholine and AMP challenge tests show significantly higher sensitivity in the diagnosis of EIB (90%), but a positive result of an AMP bronchial challenge test is characterized by higher specificity than the methacholine test (67 *v.* 40%).

Table 4. Occurrence of symptoms in EIB(+) and EIB(–) groups

Parameter	EIB(+) n (%)	EIB(–) n (%)	p
Dyspnea at rest	7 (70)	14 (44)	NS
Exertional dyspnea	10 (100)	16 (50)	0.01
Wheezes during exercise	4 (40)	3 (9)	NS
Post-exercise wheezes	10 (100)	8 (25)	< 0.001
Cough during exercise	2 (20)	3 (9)	NS
Post-exercise cough	8 (80)	8 (25)	0.006
Chest tightness during exercise	1 (10)	5 (16)	NS
Post-exercise chest tightness	5 (50)	3 (9)	0.02
Symptoms during summer time	7 (70)	13 (41)	NS
Symptoms during winter time	10 (100)	16 (50)	0.01

Table 5. Predictive value of chosen indices for the diagnosis of exercise-induced bronchoconstriction with the criterion $\Delta FEV_1max\% \geq 15\%$ (n = 42)

	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)	LR
Symptoms	80	87	67	93	6.4
Methacholine	90	40	32	93	1.5
Adenosine monophosphate	90	67	47	96	2.9
Methacholine + symptoms	70	90	70	91	7.5
Adenosine monophosphate + symptoms	70	94	78	91	11.2

PPV — positive predictive value; NPV — negative predictive value; LR — likelihood ratio; symptoms: dyspnea, wheezes an post-exercise cough

Our analysis indicates that the combination of typical symptoms (at the same time: occurrence of dyspnoea, wheezing, and coughing after exercise) and a positive result of AMP bronchial challenge test demonstrates the greatest usefulness in the diagnosis of EIB, with the sensitivity of 70%, specificity of 94%, PPV of 78%, NPV of 91%, and LR of 11.2. Table 5 shows a summary of the data on sensitivity, specificity, predictive value, and likelihood ratio for all tests used in the EIB diagnosis.

A similar analysis conducted for the $\Delta FEV_1max\%$ criterion of at least 10% showed reduced sensitivity, which supports the hypothesis that the 15% cut-off point is in fact more diagnostic for EIB (Table 6).

Discussion

In the literature, incidence of EIB in asthmatic patients is estimated at 40–90% [1, 5]. The GINA report does not present epidemiological data regarding EIB in patients with asthma or the diagnostic criteria for this condition [10]. In our group of asthma patients, the frequency of EIB was relatively low. This could be a result of the selection process — 13 out of 19 subjects were diagnosed with episodic and mild chronic asthma. Cabral et al. [14] studied 164 children subjects were diagnosed with episodic, mild, moderate, or severe chronic asthma and demonstrated a correlation between the occurrence of EIB and severity of asthma. Despite the fact that the studied group was significantly larger, the frequency of EIB was 45% (diagnostic criterion for post-exercise FEV_1 reduction ≥ 10%). EIB was least common in patients with episodic asthma (27%) and most common in patients with moderate chronic asthma (70%). Polish researchers corroborated the usefulness of the exercise test in diagnosing and monitoring of asthma [15].

However, Lex et al. [16] who assessed the value of the exhaled nitrous oxide concentration and the symptom questionnaire in the diagnosis of EIB demonstrated a relatively small incidence of this condition (14% out of a group of 85 children with asthma), but that could result from two reasons: children with episodic asthma comprised almost

Table 6. Predictive value of chosen indices for the diagnosis of exercise-induced bronchoconstriction with the criterion $\Delta FEV_1max\% \geq 10\%$ (n = 42)

	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)	LR
Symptoms	67	87	67	87	5,0
Methacholine	92	43	39	93	1,6
Adenosine monophosphate	83	70	53	91	2,8
Methacholine + symptoms	58	90	70	84	5,8
Adenosine monophosphate + symptoms	58	93	78	85	8,7

Abbreviations below the Table 5; symptoms: dyspnea, wheezes and post-exercise cough

half of the group, and some children were treated with inhaled glucocorticosteroids, what could have significantly modified the response to physical exercise. In our study, none of the patients with episodic asthma was diagnosed with EIB. Exercise-induced bronchospasm occurred in 2 of 7 patients with mild asthma and 5 of 6 patients with moderate asthma, suggesting a correlation between the occurrence of EIB and the severity of asthma. It is also important that, contrary to the studies mentioned previously, none of the patients in our study was taking anti-inflammatory medications, what makes the assessment of the relationship between asthma severity and occurrence of EIB much easier.

We observed significant differences between the patients with asthma and other groups in terms of the results of bronchial challenge tests: patients from group A had significantly lower PC_{20} values for methacholine and AMP and a significantly higher percentage of FEV_1 reduction. All asthma patients had a positive result of methacholine challenge, and the results of AMP challenge were positive in as many as 16 patients. Results of AMP bronchial challenge tests were negative in 3 asthma patients (episodic asthma). On the other hand, in group D, only 3 patients had a positive result of methacholine challenge; in 2 of them the result of AMP challenge were positive and these 2 patients were ultimately diagnosed with EIB. The results of the lung function, biochemical, and skin tests suggest that in those 2 patients EIB may be the only manifestation of asthma.

The results of methacholine challenge were positive in 5 patients from the control group. Hyperreactivity of the bronchi in response to non-specific stimuli may also occur in healthy subjects. It may be associated with respiratory tract infections or co-morbidities such as allergic rhinitis. One of the inclusion criteria for the study was a sufficiently long period of time since the last respiratory tract infection. An accepted interval of 8–12 weeks seems appropriate to exclude bronchial hyperresponsiveness following infection. It should be noted that there was one subject in the control group with a history of nasal polyps, who denied any symptoms from the respiratory tract, and this subject was diagnosed with bronchial hyperresponsiveness on methacholine (PC_{20} = 0.91 mg/ml) and AMP challenge (PC_{20} = 119.51 mg/ml). A positive result of the AMP challenge in this subject may be the result of coexisting nasal polyps and allergic rhinitis. Taking into consideration the family history (grandfather probably suffered from asthma) and the results of additional examinations (positive skin tests but total IgE concentration within normal limits), it seems that, according to some data from literature [17], despite the lack of symptoms from the respiratory tract, this subject is at risk of developing asthma and requires further observation.

As mentioned previously, some authors point to the great value of AMP bronchial challenge test in EIB diagnosis [3, 5, 11]. No publications were found confirming this point of view. Therefore, we attempted to assess the usefulness of this test in comparison to the exercise challenge test, which is still considered the "golden diagnostic standard".

The following were used to evaluate the diagnostic usefulness of the tests: the most common symptoms declared in the questionnaire (i.e. dyspnoea, cough, and wheezing after exercise), results of the AMP and methacholine bronchial challenge tests, and compilations of symptoms with the results of hyperreactivity tests. Taking into consideration the lack of a uniform definition of a cut-off point for the diagnosis of EIB, predictive values for individual tests were calculated separately for the criteria of FEV_1 reduction by 15% and 10% after completion of exercise challenge.

Results of previous studies demonstrated an inadequate effectiveness of the symptom questionnaire as a screening test for suspected EIB [18, 19]. In our study, the occurrence of a group of symptoms typical for EIB was characterized by an 80% sensitivity and 87% specificity in EIB diagnosis. Lex et al. [16] assessed the sensitivity and specificity of symptoms in EIB diagnosis in asthmatic patients not treated with glucocorticosteroids at, 75% and 59% respectively. Such disparities may come from the fact that those authors considered only symptoms occurring in a 2-week period prior to the questionnaire study, while participants of our study were asked to evaluate the intensity of symptoms during 6–12 months before the study.

On the other hand, Henriksen et al. [20] studied the correlation between the occurrence of wheezing induced by exercise and diagnosis of EIB in a group of patients complaining of symptoms exclusively or mainly after exertion. The authors, defining EIB as post-exercise FEV_1 reduction by at least 10%, diagnosed exercise-induced airway constriction in only 33% of subjects 21 of 63 and application of a more rigorous criterion of 15% FEV_1 reduction lowered the frequency of EIB diagnosis to 11%. The severity of bronchoconstriction was similar regardless of whether the subject complained of symptoms at the end of physical exertion or not. The severity of dyspnoea according to Borg's scale did not correlate with reduction of FEV_1. The authors point to the fact that as many as 6 out of 7 subjects with at least 15% reduction in FEV_1 complained of wheezing at the end of the exercise test, but the final conclusion was that wheezing reported by patients is a poor predictor of EIB [20]. Our results suggest that cough, wheezing, and chest tightness that appear immediately after exertion are more characteristic for EIB than symptoms reported during the exercise (Table 4).

In our study, bronchial challenge with methacholine and AMP were characterized by a relatively high sensitivity (90%) but low specificity. The worst results were for the methacholine test, which was associated with a specificity of 40%, PPV of 32%, NPV of 93%, and LR of 1.5, suggesting that this test may only be useful in excluding EIB. The greatest diagnostic value was found the combination of typical symptoms and a positive AMP challenge. Sensitivity of 70%, specificity of 94%, and a very high LR value, of 11.2, suggest that the presence of typical symptoms and a positive AMP challenge may be used for diagnosis of EIB, although they will not completely replace an exercise test.

Anderson et al. [21], who compared the predictive values of bronchial challenge tests with methacholine and mannitol in EIB diagnosis in patients with mild asthma, determined the sensitivity and specificity for methacholine at 67.4% and 66.1%, respectively (cut-off point for FEV_1 reduction for the diagnosis of EIB ≥ 15%). The authors point to a variable exercise-induced bronchial reactivity — during a second exercise test, EIB was diagnosed in an additional 44 (11.7%) of 375 subjects [21].

The search for diagnostic tests allowing for easier identification of EIB is being conducted in various directions. There are attempts to use the expired nitrous oxide concentration measurement (FE_{NO}), which during the last decade gained a firm place in the diagnostics and monitoring of asthma, in the EIB diagnosis [22, 23]. Buchvald et al. [24] assessed the sensitivity of FE_{NO} (cut-off point at 20 ppb) in diagnosing EIB in asthmatic children not treated with glucocorticosteroids at 71%, specificity at 76%, PPV at 53%, and NPV at 88%. However, in children treated with inhaled glucocorticosteroids, the sensitivity of the test reached as much as 100%, and NPV 96% (at FE_{NO} < 12 ppb).

EVH is another test also used for EIB diagnosis [25]. Mannix et al. [26] showed that EVH induces bronchoconstriction easier than exercise. However, it is worth noting that while this test is very useful in athletes, untrained adults and children may have difficulties acquiring ventilation at the level of 85% of maximal voluntary ventilation.

Another alternative to exercise testing is the mannitol challenge test [27–29]. Anderson et al. [30] estimated its sensitivity in EIB diagnosis to be 58.6–78.6% and specificity to be 60.8–65.2%, depending on the criterion of FEV_1 reduction (10% or 15%).

To summarize, considering variable availability of exercise testing on one hand and the potentially harmful influence of exercise-induced airway constriction on the quality of life of asthmatic patients on the other, it seems that the search for simpler and less expensive methods of diagnosing EIB is justified. It appears that some hopes may be put in the use of hyperreactivity testing to non-specific stimuli. In the population presented in this study, the highest usefulness in EIB diagnosis was demonstrated for a combination of symptoms (dyspnoea on exercise, cough, wheezing after exertion) and a positive result of AMP bronchial challenge test. Confirmation of our results on a larger population would be a valuable observation.

Conclusions

1. Occurrence of symptoms suggesting EIB alone does not have sufficient sensitivity and specificity to make the diagnosis of exercise-induced bronchoconstriction.

2. A combination of typical symptoms (dyspnoea, wheezing, cough after exercise) with a positive AMP bronchial challenge is most useful in the diagnostics of EIB.

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