SPIROGRAPHIC PARAMETERS AND THEIR CHANGE IN BRONCHIAL PATENCY VARIABILITY TESTS IN CONTROL LEVEL ASSESSMENT OF BRONCHIAL ASTHMA IN CHILDREN

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The task of bronchial asthma (BA) treatment is the control of the symptoms and the course of the disease implemented through baseline anti-inflammatory therapy. There is the necessity for objective estimation of control level using pathogenically supported techniques including the assessment of key pathophysiological features of asthma — bronchial hyperresponsiveness (BHR) and/or inflammation.

The aim of the investigation was to develop a method of control assessment objectivization based on the analysis of spirographic parameters and their change in BHR tests.

Materials and Methods. We examined 134 patients aged from 5 to 16 years with atopic BA. In addition to standard examination, we determined BA control level using ACQ-5, spirographic parameters (Master-Screen Pneumo; Germany). BHR was studied in exercise tests — pedaling 60 rpm, the stress load being 1 W/kg within 10 minutes on bicycle ergometer Kettler AX1. If initial spirogram parameters were below conditional standard, BHR was determined in a test using bronchodilator. The changes of forced expiratory volume 1-second (FEV1) under the above mentioned stimuli (exercise, bronchodilators) were statistically processed in one amount of data, and FEV1 changed under bronchodilator were taken with the sign opposite to that of the obtained result (multiplying by –1). The data were presented as M±SD, where M — mean, SD — standard deviation.

Results. Correlation coefficient in this sampling was the following: between ACQ-5 and FEV1 values R=–0.66, p<0.00001, between ACQ-5 values and BHR intensity R=–0.59, p<0.00001. FEV1 application enables to verify correctly BA control level in 64.93% of patients (coincidence with clinical verification of control level), BHR determination enables to verify control level in 60.47% of patients, and integrated use of these parameters increases the level of correct control diagnosis up to 78.29%. When the patients are grouped according to control level (complete control patients and patients with partial control level and lack of control), a part of verified cases using FEV1 increases up to 77.78%, using BHR test with indirect stimuli — up to 74.81%, using integrated assessment of these parameters — up to 86.67%.

Based on the determined regularities we developed a computer program to objectivize control level in BA patients using the analysis of initial spirographic data results and their variability in tests with bronchodilators or indirect stimuli. The program enables to assess objectively a control level in particular patients engaging pathologically significant BA markers under real-life clinical setting.

Key words: bronchial asthma; spirographic parameters; bronchial hyperresponsiveness; ACQ-5.

Currently, bronchial asthma (BA) management aims at attaining control over the symptoms and the course of the disease realized mainly during a baseline anti-inflammatory therapy [1, 2]. In addition, the amount of medications necessary to attain control over the symptoms and the course of the disease should be minimized to avoid unwanted side effects. In this regard, there is an actual necessity for anti-inflammatory BA therapy

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assessment from a perspective of attained control on the ground of available and save techniques based on current understanding of asthma pathophysiology. The preference is given to the use of markers reflecting key pathophysiological asthmatic characteristics — bronchial hyperresponsiveness (BHR) and/or inflammation.

BA is characterized by bronchial patency variability, which can be assessed in bronchodilator tests (if initial spirographic parameters are decreased) and in bronchial challenge tests (BHR test). Bronchial challenge tests, in their turn, can be performed using direct and indirect stimuli. Fundamental differences between them are pathogenetic mechanisms due to which bronchoconstrictor response is formed [3]. Inhalation of histamine, metacholine and their analogs is used as direct stimuli. These substances have an effect directly on corresponding receptors of bronchial smooth muscles resulting in their constriction in asthmatic patients, who are likely to be hypersensitive to these agents [4, 5]. The mechanisms due to which bronchocontrictor effect is realized in response to these stimuli, have no direct dependence on respiratory inflammation, but can be associated with remodeling processes or genetic peculiarities [6]. Hyperresponsiveness to direct stimuli changes slightly in the course of a baseline anti-inflammatory therapy, when low and medium doses of anti-inflammatory agents are used, however, it can be slightly reduced if high-dosage inhaled glucocorticosteroids (IGCS) are used that bears the risk of unwanted side effects [4, 5].

As indirect stimuli in bronchial challenge tests there are used exercise stress, dry air hyperventilation, inhalation of hyperosmolar aerosol, as well as adenosine monophosphate pharmacological agent. Bronchial constriction mechanisms in this type tests are due to provoked release of mediators from inflammatory cells in airways including histamine, prostaglandins, leukotrienes [7–9]. This BHR type is more of interest clinically, since the most BA attacks in everyday life are caused by the stimuli, which have an indirect effect. Hyperresponsiveness to indirect stimuli fall under reduction in the course of a baseline anti-inflammatory therapy using small and medium doses of anti-inflammatory agents, the safety of these doses has been recorded [8].

Thus, there are two BHR components: a variable component reflecting the inflammation of airway determined by means of indirect stimuli, and a fixed component reflecting airway remodeling and/or patient's genetic peculiarities determined by direct stimuli [10].

The use of indirect stimuli for BHR assessment during the management can be used to estimate the therapy efficiency and taken into account when making a decision on treatment correction towards its intensification, or on the contrary, its volume reduction. Such an approach can lead to BA management optimization using minimal dose therapy according to GINA requirements [2, 3].

In the previous studies [11] we demonstrated BA patients to have statistically significant correlation relationship between spirogram parameters and the intensity of bronchial patency variability changes in BHR assessment tests, on the one hand, and the results of control assessment according to ACQ-5 and ACT-C, on the other hand. In addition, correlation relations of values of the mentioned objective parameters with ACQ-5 findings were higher than with ACT-C findings. Taking into consideration that in ACQ-5 tests BA symptoms are assessed for a week, and in ACT-C tests — for a month, it can be believed that dynamics of functional parameters and BHR using indirect stimuli under current BA therapy in children is close to a "week" period.

On this basis, complex assessment of spirographic parameters and the intensity of their changes in BHR tests can be considered as a pathogenetically grounded method to assess BA control level dynamics in children.

The aim of the investigation was to develop an objective assessment method of bronchial asthma level based on the analysis of spirographic parameters and their changes in bronchial patency variability tests.

Materials and Methods. We examined 134 patients aged from 5 to 16 years with primarily atopic BA and different BA control. All children received treatment in accordance with the disease period and its severity in compliance with the existing recommendations [1]. The patients underwent standard clinical, allergological, immunological and functional examination, and tests to assess BA control level using Asthma control questionnaire — 5 (ACQ-5) compared with objective test data (the patients were examined by an experienced clinician). Spirographic study was performed using Master-Screen Pneumo (Jaeger, Germany). The parameters were assessed by comparing with a standard norm [12].

The study complies with the declaration of Helsinki (adopted in June, 1964 (Helsinki, Finland) and revised in October, 2000 (Edinburg, Scotland)), and was performed following approval by the ethic committee of I.M. Sechenov First Moscow State Medical University (Russia). Written informed consent was obtained from all patients aged 15–16 and the parents of those patients who were under 15 in accordance with the Federal Law "The Basic Law on the Health Protection of the citizens of the Russian Federation" dated July, 22, 1993 No.487-1.

We studied bronchial hyperresponsiveness in exercise tests (pedaling on bicycle ergometer Kettler AX1 (Germany) with velocity of 60 rpm and load of 1 W/kg within 10 minutes). We assessed the dynamics of spirographic data on 5–10 minutes after exercise compared to pre-exercise value of spiroraphic parameters. Exercises were performed by children, whose initial spirogram findings had been within the limits of a conditional standard [13]. If initial spirogram parameters were below the conditional norm, as well as in children receiving therapy due to exacerbation, we determined bronchial obstruction variability in tests with a bronchodilator (Salbutamol — metered aerosol through a spacer). In addition, we compared initial spirographic parameters with those recorded 20 minutes after inhalation of bronchodilator age dosage. The changes of spirographic parameters were assessed by a formula (N–A)/A(%), where A — initial values of a spirographic parameter; N — a parameter value after exercise test or a test with a bronchodilator.

The changes of forced expiratory volume 1-second (FEV1) under the above mentioned stimuli (exercise, bronchodilators) were statistically processed in one amount of data, and FEV1 changed under bronchodilator were

taken with the sign opposite to that of the obtained result (multiplying by –1).

The data were presented as M±SD, where M — mean, SD — standard deviation. Statistical analysis was performed using Statgraphics plus program.

Results and Discussion. According to ACQ-5 data, 76 children at the moment of examination had complete control of the disease symptoms (ACQ-5<0.75 scores, mean test value — 0.25±0.24 scores). 37 patients were diagnosed a partial control (ACQ-5 — from 0.75 to 1.5 scores, mean test value — 1.02±0.24 scores), and 23 children lacked BA control (ACQ-5>1.5 scores, mean test value — 2.49±0.71 scores).

Mean FEV1 in patients with a complete BA control according to ACQ-5 assessment in the sampling under study was 102.90±11.30%, in patients with a partial control — 89.55±11.39%, in children lacking control — 69.77±14.39%. The differences between the groups were statistically significant, F=68.7; p<0.00001. Correlation coefficient (the correlation between ACQ-5 and FEV1) was rather high and in this sampling it was R=–0.66 (F=102.7; p<0.00001). Table 1 demonstrates the detailed statistics of FEV1 (% of standard norm) in children with different BA control level determined by ACQ-5.

Table 1

Statistical data on FEV1 (% of a standard norm) in children with different bronchial asthma control level assessed in accordance with ACQ-5

Statistic parameters	ACQ<0.75 scores	0.75<ACQ<1.5 scores	ACQ>1.5 scores
Total patients	76	37	21
Mean	102.92	89.55	69.76
MSD	11.30	11.39	14.04
Median	102.50	89.00	72.27
Minimum–maximum	81.00–132.00	66.00–107.00	43.00–95.00
95% CI	96.86–105.50	85.75–39.35	63.34–76.17

Note: MSD — mean square deviation; CI — confidential interval.

Table 2

Discriminative analysis findings - verification of bronchial asthma control according to functional studies, compared to ACQ-5 findings (three control levels were distinguished)

Parameter	Number of verified cases, %	χ^2	p
FEV1	64.93	93.07	<0.00001
Bronchial patency variability	60.47	62.31	<0.00001
FEV1 and bronchial patency variability	78.29	120	<0.00001

Table 3

Discriminative analysis findings - verification of bronchial asthma control according to functional studies, compared to ACQ-5 findings (two control levels were distinguished: complete control and a combined group "partial control + lack of control")

Parameter	Number of verified cases, %	χ^2	p
FEV1	77.78	68.17	<0.00001
Bronchial patency variability	74.67	35.67	<0.00001
FEV1 and bronchial patency variability	86.67	80.14	<0.00001

Bronchial patency variability in the same patients was analyzed in BHR tests (bronchial challenge exercise tests) and in tests to reveal bronchial obstruction variability with a bronchodilator (taking into consideration an initial clinical status and spirogram findings). FEV1 changes at ACQ<0.75 scores were –3.22±7.42%, at ACQ from 0.75 to 1.5 scores — –10.24±10.45%, at ACQ>1.5 scores — –27.08±17.40% (F=40.31; p<0.00001).

The findings indicate that, generally, as BA control level goes down there is the appropriate growth of bronchial patency variability. Moreover, mean values of FEV1 changes under the influence of stimuli in patients with complete and partial BA control do not exceed 10% that is actually a norm variant. In the lack of control, mean values appear to be beyond the limits. Correlation coefficient of ACQ-5 values and the intensity of bronchial patency variability was R=–0.59 при p<0.00001.

We performed a discriminative analysis to assess a potential contribution of functional parameters into the disease control diagnostics (Table 2).

FEV1 use enabled to verify BA control level in 64.93% patients (the coincidence with clinical verification of control level), BHR determination enables to verify correctly control level in 60.47% patients, and integrated use of these parameters increases a correct diagnostic control level up to almost 80%.

When the patients are grouped according to control level (complete control patients and patients with partial control and the lack of control), a part of verified cases using FEV1 increases up to 77.78%, using BHR test with indirect stimuli — up to 74.81%, using integrated assessment of these parameters — up to 86.67% (Table 3).

In order to optimize an integrated assessment of BA control level taking into consideration objective data obtained using pathologically significant investigation techniques (analysis of initial spirographic findings and variability of spirographic data in tests with bronchodilators or indirect stimuli) we developed a computer program, which enables within the accuracy of 86.7% to refer a child to a group of BA complete control or incomplete control or the lack of control [14]. The program (Fig. 1) is based on the analysis of initial spirographic indices (FEV1 — percentage of the standard norm) and the intensity of their changes in bronchial obstruction variability tests with bronchodilators (the percentage of spirographic parameter changes is taken with the opposite sign) or in BHR tests with indirect stimuli (in this study — exercise tests). The program enables to make an objective assessment of control level simply and rapidly with the assistance of pathologically significant BA markers.

Along with personal data, in appropriate program sections there should be filled in initial FEV1 values — percentage of a standard norm and the intensity of FEV1 changes —

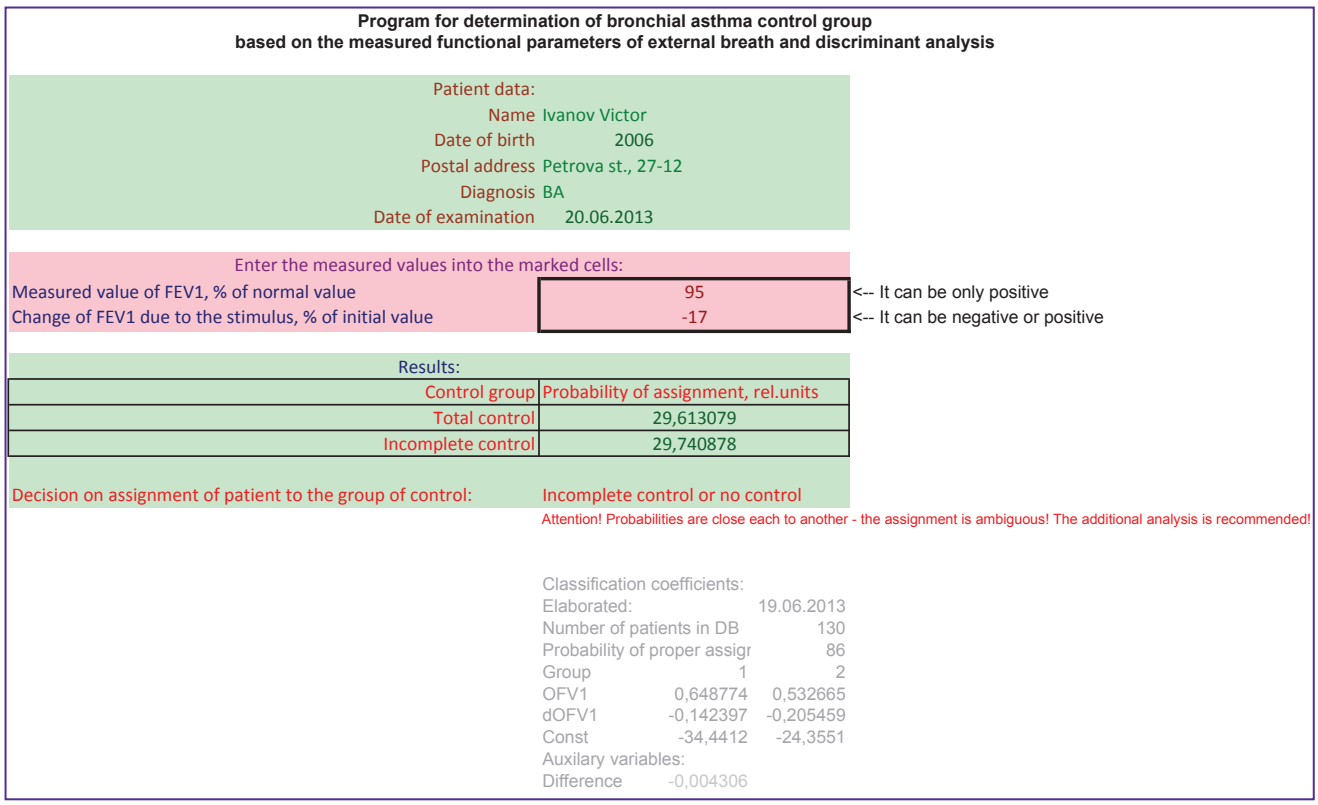

Fig. 1. Work window appearance of BA control level assessment program based on the data analysis of functional studies. A patient's personal data are arbitrary

Table 4

Pharmacoeconomic analysis of functional studies used in bronchial asthma control level assessment

CER coefficients for functional studies — cost of 1% of verified cases			
Investigation	**Effectiveness, E, %**	**One research cost, dC, RUR**	**CER**
Bronchial patency variability	74.7	48.8	0.7
FEV1	77.8	34.1	0.4
Integrated assessment (FEV1 + bronchial patency variability)	86.7	80.8	0.9
ICER coefficients of the technique under analysis (an integrated assessment of FEV1 and bronchial patency variability) in relation to comparison methods (FEV1 or bronchial patency variability)			
Comparison techniques	**Effectiveness difference dE, %**	**Difference in cost, dC, RUR**	**ICER**
FEV1	8.9	46.6	5.2
Bronchial patency variability	12.0	32.0	2.7

as percentage of initial values after bronchial patency variability tests (bronchial obstruction variability tests with bronchodilators — the values of spirographic parameter changes are taken into consideration with opposite signs (multiplying by –1) and bronchial challenge tests with indirect stimuli — in this case with controlled exercise).

Then with 86.7% probability we calculated BA control level (control is attained — complete control, or control is not attained — incomplete control).

The developed program is based on discriminative analysis of 134 observations; the program can be improved as additional observations are collected.

Using a cost–effectiveness analysis we performed a pharmacoeconomic analysis of functional studies used when determining BA control level including FEV1, bronchial patency variability, and their integrated determination. Table 4 and Fig. 2 represent the analysis findings.

When carrying out the analysis we calculated the following indices:

1. Effectiveness unit — E (%); in the case under

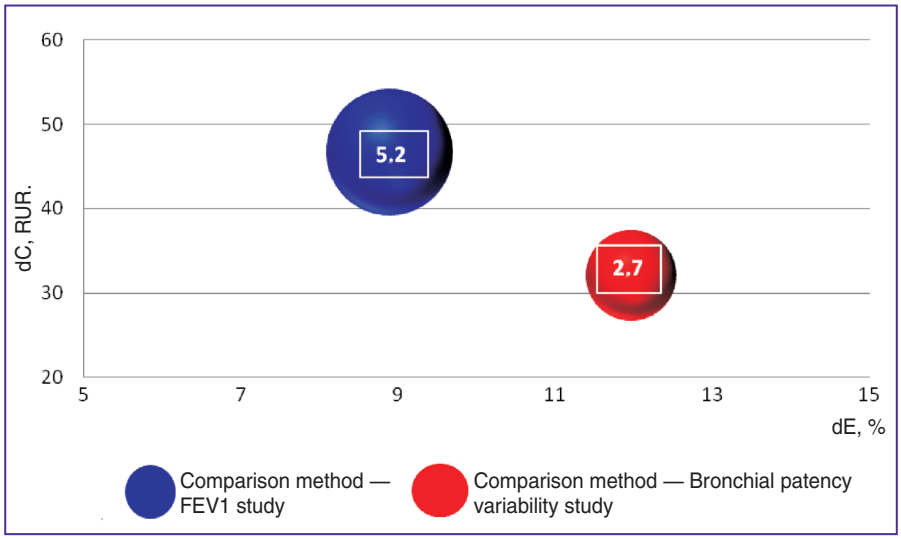

Fig. 2. Pharmacoeconomic analysis of functional studies using incremental cost-effectiveness ratios (ICER) of the analyzed method (integrated assessment of FEV1 and bronchial patency variability) in relation to comparison methods (FEV1 or bronchial patency variability). X-axis values indicate the effectiveness difference of the method under analysis and a comparison method — dE, %, Y-axis values — cost differene of the method under analysis and a comparison method — dC, RUR. Ball size and value — ICER, it indicates the value of costs, which should be paid in full for each unit of verified cases in relation to a comparison method

consideration — the proportion (%) of verified control level cases when particular functional studies are used.

2. The cost of one functional study in native currency — C (RUR); includes the expenditures on personnel, appreciation of basic and optional equipment; takes into account procedure time. General and administrative costs were taken for const and were neglected when calculating study cost.

3. Difference in the effectiveness of the analyzed method in relation to a comparison method — dE (%). As an analyzed method we considered the study characterized by higher clinical effectiveness (integrated assessment of FEV1 and bronchial patency variability), and as comparison methods — the investigations, effectiveness of which is exceeded by the analyzed technique (the assessment of particular characteristics — FEV1 or bronchial patency variability);

4. Difference in cost of the analyzed technique compared to a comparison method in native currency – dC (RUR).

The calculated indices were used to determine the following coefficients:

1. CER (cost-effectiveness ratio) — "cost-effectiveness" ratio. It indicates effectiveness unit cost. In the case under study it is the cost of 1% of verified cases; a minimum value provides maximum effect at minimum cost.

2. ICER (incremental cost-effectiveness ratio) — incremental cost to increment effectiveness ratio of the method under analysis in relation to a comparison method. It demonstrates the value of costs necessary for effectiveness increase by 1%.

Minimum cost of effectiveness unit is observed when routine spirometry is used (FEV1 determination) — 0.4 RUR for 1% effectiveness per one study. Effectiveness unit cost in integrated assessment of FEV1 and bronchial patency variability, which have the best "clinical effectiveness" indices of control level verification, is the highest (0.9–1.0 RUR per effectiveness unit), but comparable with effectiveness unit cost of bronchial patency variability study (0.7–0.8 RUR per effectiveness unit).

The selection of study consisting in an integrated assessment of FEV1 parameters and bronchial patency variability, which has higher clinical effectiveness compared to the study of separate characteristics (FEV1 or bronchial patency variability), will require extra investments for each study to improve effectiveness by 1%:

in comparison with bronchial patency variability study — 2.7 RUR;

as compared with FEV1 determination — 5.2 RUR.

Thus, in spite of the fact that an integrated assessment of FEV1 and bronchial patency variability is clinically more advantageous, its practical use will require additional investments compared to the study of separate parameters. However, real difference in the cost of integrated control level assessment compared to the study of separate characteristics (dC, RUR) is not high and comparable with the cost of a daily dosage of anti-inflammatory drug combination frequently administered as BA baseline therapy (Budesonide + Formoterol, Salmeterol + Fluticasone) — depending on a dosage — 30.2–42.8 and 18.0–35.3 RUR market price, respectively.

Conclusion. Integrated assessment of spirometric parameters and the intensity of their changes in bronchial challenge tests with indirect stimuli (exercise) or in bronchodilator tests enabled to verify bronchial asthma control level in 78.29% of patients by dividing control levels into: complete, partial and the lack of control; and in 86.67% of patients by grouping them into complete control group and a joint group "partial control + the lack of control". The determined regularities enabled to develop a computer program to objectivize control level in bronchial asthma patients using an integrated analysis of initial spirographic data and bronchial hyperresponsiveness in particular patients to be used under real-life clinical setting.

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