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

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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 М±SD, where М — 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.
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 spiographic 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 bronchoconstrictor 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 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].

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 spiographic 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 spiographic 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 spiographic data on 5–10 minutes after exercise compared to pre-exercise value of spiographic 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 spiographic parameters with those recorded 20 minutes after inhalation of bronchodilator age dosage. The changes of spiographic parameters were assessed by a formula (N–A)/A(%), where A — initial values of a spiographic 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.
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 spirometry 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 spirometry findings and variability of spirometric 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 spirometric indices (FEV1 — percentage of the standard norm) and the intensity of their changes in bronchial obstruction variability tests with bronchodilators (the percentage of spirometric 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 —
as percentage of initial values after bronchial patency variability tests (bronchial obstruction variability tests with bronchodilators — the values of spiographic 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

<table>
<thead>
<tr>
<th>Patient data:</th>
<th>Name</th>
<th>Ivanov Victor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of birth</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Postal address</td>
<td>Petrova st., 27-12</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>BA</td>
<td></td>
</tr>
<tr>
<td>Date of examination</td>
<td>20.06.2013</td>
<td></td>
</tr>
</tbody>
</table>

Enter the measured values into the marked cells:

| Measured value of FEV1, % of normal value | 95 |
| Change of FEV1 due to the stimulus, % of initial value | -17 |

Results:

<table>
<thead>
<tr>
<th>Control group</th>
<th>Probability of assignment, rel.units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total control</td>
<td>29,613079</td>
</tr>
<tr>
<td>Incomplete control</td>
<td>29,740878</td>
</tr>
</tbody>
</table>

Table 4
Pharmacoeconomic analysis of functional studies used in bronchial asthma control level assessment

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Effectiveness, E, %</th>
<th>One research cost, dC, RUR</th>
<th>CER</th>
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<tr>
<td>Bronchial patency variability</td>
<td>74.7</td>
<td>48.8</td>
<td>0.7</td>
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<tr>
<td>FEV1</td>
<td>77.8</td>
<td>34.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Integrated assessment (FEV1 + bronchial patency variability)</td>
<td>86.7</td>
<td>80.8</td>
<td>0.9</td>
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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)

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<tr>
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<th>Effectiveness difference dE, %</th>
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<th>ICER</th>
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<tr>
<td>FEV1</td>
<td>8.9</td>
<td>46.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Bronchial patency variability</td>
<td>12.0</td>
<td>32.0</td>
<td>2.7</td>
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</table>

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

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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 spiographic data and bronchial hyperresponsiveness in particular patients to be used under real-life clinical setting.

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**References**


