ANALYSIS OF THE POSSIBILITIES OF THE FLOW-VOLUME CURVE ASSESSMENT BY THE CHANGES IN ITS SHAPE IN PATIENTS WITH OBSTRUCTIVE AIRWAY DISEASES

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In case of obstructive disorders, the flow-volume curve has a concave shape, but this feature is not given due attention. The analysis of the velocity indicators of the respiratory function (such as the peak expiratory flow (PEF) and forced expiratory flows (FEFs)) will significantly expand the diagnostic capabilities of the spirometry method. This paper aims to perform a comparative analysis of the diagnostic strength of the methods of the flow-volume curve assessment by the changes in its shape in patients with obstructive airway diseases to determine the most reliable one. The respiratory function of 540 patients was tested (234 are men (57 [36; 67] years) and 306 are women (59 [44; 69] years)), with the ratio of areas under the actual curve and the predicted curve calculated for each one, as well as the angle formed by the curve; the ratio of the actual FEF (henceforth referred to as FEF) to the predicted FEF, cut-off points to differentiate between obstructive diseases and health. On the basis of these results, we concluded whether the patient's bronchi were blocked. The results were then compared to the Knudson reference equations, with the test's operational characteristics calculated compared to the standard. The methods of assessing the angle β and the total concavity of the flow-volume curve have high diagnostic sensitivity (87.8% and 95.6% respectively). The assessment of the area under the curve (AEX-FV) has high diagnostic specificity (88.6%). The results obtained show sufficient diagnostic efficiency of the methods of flow-volume curve estimation by the changes in its shape. However, the use of these methods in isolation from the reference equations does not currently seem reasonable for clinical practice. It appears reasonable to use the reference equations and one of the methods of curve shape assessment together.

Keywords: spirometry, respiratory function, flow-volume curve

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АНАЛИЗ ВОЗМОЖНОСТЕЙ МЕТОДА ОЦЕНКИ КРИВОЙ «ПОТОК–ОБЪЕМ» ПО ИЗМЕНЕНИЮ ЕЕ ФОРМЫ ПРИ ОБСТРУКЦИИ БРОНХОВ

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При обструкции бронхов кривая «поток-объем» имеет характерную вогнутую форму, однако данному признаку не уделяют должного внимания. Анализ скоростных показателей функции внешнего дыхания (ФВД), таких как пиковая объемная скорость выдоха (ПОС) и максимальные объемные скорости выдоха (МОС), позволит расширить диагностические возможности спирометрии. Цель работы — провести сравнительный анализ диагностической эффективности методов оценки кривой «поток-объем» по изменению ее формы на фоне обструктивных нарушений. Оценено 540 проб ФВД пациентов (234 мужчины 57 [36; 67] лет и 306 женщин 59 [44; 69] лет), для каждого определено процентное отношение площадей под фактической кривой и кривой предполагаемой нормы, рассчитан угол, образованный кривой, определено процентное отношение фактических МОС с предположительно нормальными, рассчитаны отрезные точки с целью разграничения обструктивных нарушений и нормы. Сформировано заключение о наличии или отсутствии у пациента обструкции бронхов. Результаты сравнивали с заключениями, полученными с помощью системы Knudson, с расчетом операционных характеристик теста относительно стандарта. Показано, что методы оценки угла β и общей вогнутости кривой обладают высокими значениями чувствительности (87,8% и 95,6% соответственно), а оценка площади под кривой «поток–объем» (AEX-FV) обладает высоким значением специфичности (88,6%). Таким образом, продемонстрирована достаточная диагностическая эффективность методов оценки кривой по изменению ее формы. Однако использование этих методов в отрыве от принятых систем расчета должных не видится целесообразным. Логичным представляется совместное использование системы расчета должных и одного из методов оценки кривой по форме.

Ключевые слова: спирометрия, ФВД, кривая «поток-объем»

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In patients with obstructive airway diseases the flow-volume curve is characteristically concave to the X axis, with the level of concavity correlating with the severity of the airway obstruction [1–3]. In practice, however, the changes in the shape of the curve are often ignored when interpreting the results, with only the difference between the patient's respiratory function test results and the approximated values taken into account [1]. Even if the shape is assessed, it is assessed visually, as proper mathematical parameters for assessing concavity have not yet been accepted into clinical practice. Eye estimates

are obviously very subjective, because the method requires a certain level of experience and qualifications from the medical professional. Furthermore, it's not rare for the concavity to still be present even when the the patient's respiratory function score falls over 100% of the predicted score, showing a lack of any respiratory dysfunction. If that's the case, even though the patient's life history together with the characteristic shape of the curve might suggest otherwise, these points will not be reflected in the diagnosis, making it impossible to objectively evaluate the patient's condition.

It is also worth noting that diagnosing the patient using only some of the respiratory function scores (including the forced expiratory volume in one second (henceforth referred to as FEV1) decrease rate, the FVC or VC (vital and forced vital capacities) decrease rate and the Tiffno and Gensler indices), on the one hand, decreases the time needed to interpret the results of one test, but, on the other, artificially narrows the clinical possibilities of spirometry. In routine practice, the air flow rate is often not considered, even though it shows the condition of the bronchial tree by levels [3] and could provide a clearer understanding of the patient's condition without resorting to the use of expensive and time-consuming diagnostic procedures (such as chest X-ray or bronchoscopy).

Attempts have been made to make the visual assessment of the curve more objective through analysing additional parameters calculated from the flow-volume curve. For example, one review paper considers several parameters, i.e. evaluation of the angle formed by the curve, evaluation of the area ratio (AEX-FV) and evaluation of the degree of deviation of the actual FEF values from the ones approximated by the authors [4]. However, despite the scientific community's interest in the methods described [5–8], as of today, there is still no definitive understanding of their effectiveness in clinical practice. Therefore, this study aims to conduct a comparative analysis of the diagnostic efficiency of the methods of the flowvolume curve assessment based on changes in its shape in patients with obstructive airway diseases in order to determine the most reliable one.

METHODS

The materials for this study were collected from patients of the Research and Clinical Centre No. 2 of the Petrovsky Russian National Research Center. The following criteria for inclusion in the study were used: seeking medical attention due to conditions included in the J00-J99 ('Diseases of the respiratory system') and Z00-Z99 ('Factors influencing health status and contact with health services') ICD-10 code ranges; the patient's consent to tests; the spirometry test complies with the quality standards required by the European Respiratory Society and the American Thoracic Society (ATS/ERS standards) [9], adopted by the Russian Respiratory Society [1]; the patient is over 18.

540 patients were selected, of whom 234 (43.3%) were male and 306 (56.7%) were female. The mean age was 57 [36; 67]

years in men and 59 [44; 69] years in women. To understand the efficiency of the considered methods in patients of different ages, the sample group was divided into 10-year age intervals. The 18–30 years group included 76 patients, the 31–40 years group included 50 patients, the 41–50 years group included 57 patients, the 51–60 years group included 109 patients, the 61–70 years group included 134 patients, the 71–80 years group included 93 patients, and the 81–90 years group included 21 patients.

For each patient:

1) the presence or absence of bronchial obstruction was determined (by calculating the Tiffno or Gensler index);

2) if obstruction was present, its the degree was determined (by the decrease in the patient's FEV1 relative to the Knudson reference equations);

3) the percentage ratio of areas under the actual flow-volume curve and the assumed normal curve was determined;4) the angle formed by the curve was calculated;

5) the percentage ratio of the actual and estimated normal FEF was determined.

Respiratory function test results were saved in MS Excel software (USA). The following patient data were recorded: sex and age; height and weight; results of slow vital capacity tests (VC); results of forced vital capacity tests (forced air flow volume and rate, as well as calculated Tiffno and Gensler indices).

Lagrange interpolation was used to calculate the function for the downward part of the flow-volume curve. It was demonstrated that for a curve with interpolation nodes at PEF, FEF_{25} , FEF_{50} , FEF_{75} and FVC, the interpolation function is the following:

$$P_{p}(x) = ax^{4} + bx^{3} + cx^{2} + dx + e,$$
(1)

where *a*, *b*, *c*, *d*, *e* are the coefficients of the interpolation polynomial calculated individually for each patient.

The numerical integration of the above function was used to calculate the AEX-FV. The definite integral of the type

$$\int_{\alpha}^{\beta} (ax^{4} + bx^{3} + cx^{2} + dx + e)dx,$$
(2)

where α , β are the boundaries of the definite integral, was approximately calculated using the left Riemann sum.

The angle β was calculated using the formula for determining the angle between two vectors with the vector dot product



Fig. 1. Calculating angle β (using FEF₅₀ angle as example).



Fig. 2. Determining the degree of deviation of actual FEF values from the predicted values (using a difference of over 200 ml between FVC and VC as example).

and vector length in coordinate form. The two vectors used for calculating the angle were vector a, defined as (FEF₅₀-PEF projection on the Y axis) and vector b, defined as (FEF₅₀-FVC) (Fig.1) [4], with FEF₅₀ or FEF₇₅ taken as FEFx. For each patient, the FEF₅₀ angle was calculated, with the angle centered on FEF₇₅ considered to be the angle β , if the actual FEF₅₀ exceeded the estimated value of the index.

Therefore, the formula for determining the angle between two vectors is the following:

$$cos(ab) = \frac{-\frac{1}{2}FVC \times (FVC - \frac{1}{2}FVC) - (PEF-FEF_{x}) \times FEF_{x}}{\sqrt{(\frac{1}{2}FVC)^{2} + (PEF-FEF_{x})^{2}} \times \sqrt{(FVC - \frac{1}{2}FVC)^{2} + (FEF_{x})^{2}}},$$
(3)

with FEF_{50} or FEF_{75} taken as FEF_{x} .

Approximate values of the air flow rate for general concavity assessment were determined using the equation of the straight line connecting the PEF and FVC points. If the difference between FVC and VC is greater than 200 ml, it is more viable to replace FVC with VC and construct a straight line connecting the PEF and VC points. Like in the previous case, the approximate values of the air flow rate will presumably be located on this straight line, but in this case they will be 1/4, 1/2 μ 3/4 FVC (not VC), because otherwise the logic of the calculations will contradict FEF₂₅, FEF₅₀ μ FEF₇₅ as defined by the Russian Respiratory Society [1], according to which each of these values is equal to the respective fraction of FVC (not VC). This method is visually represented in Fig. 2.

Our assessment of the respiratory function is based on the accepted spirometry results interpreting system, namely, calculating the percentage of the deviation of the actual value from the reference value [1, 2]. This provides for further comparison of the obtained ratio with reference intervals. Because the population size of this study was insufficient to define comparison intervals, it was decided to calculate cut-off points for each method of flow-volume curve assessment by shape that could unambiguously differentiate between healthy patients and patients with obstructive disorders in the test sample. To determine cut-off points, patients (n = 81) were selected from the primary analysis sample who were considered healthy for the purposes of this study, meaning their Tiffno index was greater than 70% [1, 2] and the visual assessment by the functional diagnosis physician did not reveal any abnormalities. The mean values of AEX-FV, angle β , and the percentages of deviation of the actual FEF values from the predicted values were calculated for the obtained test sample. These values were taken as cutoff points. Obstructive disorders were considered confirmed in patients with FEF values smaller than the cut-off points.

The testing of respiratory function by spirometry was performed on a SpiroS-100 spirometer manufactured by the Russian company AltoMedica [10]. Statistical analysis was performed by calculating the absolute and relative frequencies of occurrence of presence and absence of obstruction for each of the described methods of assessing the flow-volume curve shape with further calculation of the operational characteristics of the test relative to the standard (using contingency tables). The Knudson reference equations for respiratory function were chosen as reference in the calculation of operational characteristics because they do not have any restrictions on patients' characteristics (unlike, for example, the Clement [11, 12], GLI [13], and ECCS [14] reference equations). Statistical analysis was performed in IBM SPSS Statistics for Windows v.27.0 (USA), and MedCalc by MedCalc Software Ltd v.23.0.6 (Belguim).

RESULTS

AEX-FV

For each patient in the training sample, the area under the actual flow-volume curve (AEX-FV) was calculated by numerical

Table 1. Cut-off points for AEX-FV evaluation, calculated for the age ranges in question

Age range	Mean area ratio, %	Cut-off point, %
18–30 years	91.7 ± 5.9	86
31–40 years	91.6 ± 5.1	87
41–50 years	91.7 ± 2.7	89
51–60 years	88.9 ± 3.6	85
61–70 years	90.5 ± 4.5	86
71–90 years	82.2 ± 7.8	74

Note: mean area ratios are presented as (mean value ± standard deviation), cut-off point values are rounded to the next integer.

Age range	∠β at FEF ₅₀ , °	∠β cut-off point at FEF ₅₀ , °	∠β at FEF ₇₅ , °	∠ β cut-off point at FEF ₇₅ , °
18–30 years	166.9 ± 8.9	158	162.3 ± 6.9	155
31–40 years	170.5 ± 8.7	162	157.5 ± 8.5	149
41–50 years	170.0 ± 8.7	161	155.8 ± 7.4	148
51–60 years	169.7 ± 11.5	158	152.7 ± 5.8	147
61–70 years	169.5 ± 6.4	163	148.2 ± 6.8	141
71–90 years	171.6 ± 9.4	162	148.2 ± 6.4	142

Table 2. Cut-off points for angle β , calculated for the considered age ranges

Note: mean angle values are presented as (mean value ± standard deviation), cut-off point values are rounded to the next integer.

integration. The area under the predicted values curve was defined as the area of a right-angled triangle equal to half of the product of its cathetes, i.e.

$$S(AEX Normal) = \frac{1}{2} \times PEF \times FVC.$$
 (4)

In order to come to a conclusion about the reference figure for the percentage ratio of AEX-FV to AEX-Normal, which will allow unambiguous differentiation between healthy patients and patients with obstructive disorders, the mean value for the ratio of AEX-FV to AEX-Normal was calculated (see Table 1). Given the close cut-off point values for all age groups except patients over 70 years of age, an area ratio of 85% was taken as the single cut-off point for these age ranges (calculated as the average between the cut-off point values for the age ranges). Using the AEX-FV evaluation method, 38.1% of patients (206) were found to be healthy and 61.9% of patients (334) were found to have obstructive disorders, whereas with the Knudson reference equations the results were 31.1% of patients (168) and 68.9% of patients (372) respectively.

Angle β

The preliminary calculation of the mean angle showed that in some cases, even though the angle is within normal range and the diagnostic conclusion states the patient is healthy, the concavity of the flow-volume curve towards the X axis is characteristic of obstructive airway diseases. This is caused by a decrease in the $\ensuremath{\mathsf{FEF}_{75}}$ index, which was not previously taken into account in research papers on this issue [4,5]. For this reason, we also calculated the mean angle centred on ${\rm FEF}_{\rm 75},$ provided that the actual ${\rm FEF}_{\rm 50}$ value exceeds the predicted value. The cut-off points that allow unambiguous differentiation between healthy patients and patients with obstructive disorders are presented in Table 2. Using the angle β evaluation method, 26.9% of patients (145) were found healthy and 73.1% of patients (395) were found to have obstructive disorders, whereas with the Knudson reference equations the results were 31.1% of patients (168) and 68.9% of patients (372) respectively.

Assessment of the general concavity

As per the accepted procedure of generating an assessment report, predicted maximum flow rate values at 25%, 50% and 75% FVC were calculated for each patient, and the percentage deviation of the actual values from the approximate ones was determined. The approximate values were calculated using the following two-point form:

$$\frac{X - X_1}{X_2 - X_1} = \frac{y - y_1}{y_2 - y_1}.$$
(5)

Therefore, FEF was determined at the given levels using the following equation:

$$\mathsf{FEF}_{y} = \frac{(\mathsf{FEF}_{x} - \mathsf{PEF})_{x} \times (\mathsf{FVC}_{y} - \mathsf{PEF}_{y})}{\mathsf{FVC}_{y} - \mathsf{PEF}_{y}} + \mathsf{PEF}_{y}, \tag{6}$$

where x and y are the point's positions on the X and Y axis, respectively. It should be noted that in cases where the patient's actual FEF exceeded the predicted value, the actual value was considered normal, and the values' ratios were considered to be 100%. This does not contradict the Russian Spirometry Standards, as the approved algorithm for the evaluation of spirometry indicators allows for a percentage ratio of the actual values to predicted ones greater than 100%, with the value exceeding this mark taken as 100% and considered normal. We analysed the entire test sample in this manner, determining cut-off points for each considered age range (Table 3). Using the general concavity method, 18.5% of patients (100) were found to be healthy and 81.5% of patients (440) were found to have obstructive disorders, whereas with the Knudson reference equations the results were 31.1% of patients (168) and 68.9% of patients (372) respectively. More obstructive disorders can be detected using the general concavity method compared to the Knudson reference equations (Table 4).

DISCUSSION

The operational characteristics of AEX-FV evaluation are, in general, quite balanced, with the maximum and minimum sensitivity of the test recorded in patients from 61 to 70 years

Table 3. Cut-off points for maximum flow rate at the given FVC percentages calculated for the considered age ranges.

Age range	FEF ₂₅	FEF ₅₀	FEF ₇₅
18–30 years	0.00 [0.00; 1.61]	0.00 [0.00; 1.36]	0.00 [0.00; 2.75]
31–40 years	0.00 [0.00; 4.69]	0.00 [0.00; 11.84]	0.39 [0.00; 13.07]
41–50 years	1.51 [0.00; 7.74]	1.79 [0.00; 5.22]	10.66 [0.00; 21.19]
51–60 years	0.00 [0.00; 6.71]	0.05 [0.00; 12.36]	13.21 [1.98; 20.34]
61–70 years	0.50 [0.00; 5.35]	0.00 [0.00; 5.67]	23.53 [13.96; 36.71]
71–90 years	0.00 [0.00; 3.48]	4.86 [0.00; 14.09]	26.55 [11.08; 32.28]

Note: cut-off point values are presented as Me [Q1; Q3].

RE AEX-FV Angle β General concavity IIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	GS	Diagnosis in the patient's medical history					
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Table 4. Results of the diagnostic efficiency evaluation of the methods of estimating the flow-volume curve by shape change in the considered age ranges

Note: GS — gold standard, RE — reference equations, S — diagnostic sensitivity, Sp — diagnostic specificity.

old (0.916) and from 71 to 80 years old (0.674) respectively, and the maximum and minimum specificity recorded in patients from 18 to 30 years old (0.933) and from 61 to 70 years old (0.800) respectively. In elderly patients there is a gradual weakening of respiratory muscles, diagnosed in spirometric examination as a degree of obstruction, while the normal triangular flow-volume curve is almost never found. Thus, in elderly patients there is a characteristic difference between AEX-FV and AEX-Normal, which is natural. Given this age-specific pattern, screening for respiratory pathologies in this age range is somewhat difficult. The results can also be explained by the structure of the test sample used in this study, which included predominantly patients with confirmed respiratory pathologies, whereas to assess the screening power of the test, a large sample of healthy patients is required. In this case, it is reasonable to increase the sample heterogeneity, but due to the limited research capacity of this study, this was not possible.

The method of calculating the angle β formed by the flowvolume curve has a sufficiently high diagnostic sensitivity for all age ranges in question, indicating the significant potential of this method for diagnostics. Additionally, it has the advantage of disorder assessment by levels, unlike, for example, the previously discussed AEX-FV assessment, which evaluates the state of the bronchial tree as a whole. As for specificity, the AEX-FV values were informative in all age groups (except for the elderly and senile), while the β -angle values were not informative in most age groups. Similarly to the AEX-FV evaluation method, this can be explained by the structure of the analysed data and the higher number of sick patients compared to healthy patients.

As for the assessment of the general flow-volume curve concavity, the sensitivity of this method, similarly to the sensitivity of angle β evaluation, is consistently high for all age groups, indicating a significant quality of diagnostic conclusions based on this method. The specificity, similarly to angle evaluation, is uninformative in all considered age groups.

Therefore, all considered methods of flow-volume curve evaluation by its shape change can be used as clarifying parameters in complicated or ambiguous clinical cases due to their substantial diagnostic capabilities. To improve the quality of spirometric screening for respiratory diseases, the calculation of the ratio of the area under the actual curve to the area under the predicted curve, i.e. AEX-FV, can be used as a clarifying criterion for patients under 70 years of age.

It reasonable to be concerned that the evaluation logic inherent for the methods considered may lead to more frequent false positives compared to the traditional methodology. However, in our opinion, a false positive in the context of this Russian Respiratory Society method [1] will be understood as a hidden obstruction that is not directly detected by reference equations, Tiffno or Gensler indices, or new parameters for assessing FVC indices (in particular, the lower limit of normality (LLN) [15–17] and z-score [1, 2, 15]). It is our opinion that in this case, heightened obstructive ventilation disorder vigilance of methods of flow-volume curve assessment based on changes in its shape is justified, since hidden obstruction is considered a preclinical stage of COPD and may subsequently lead to respiratory failure [18].

CONCLUSIONS

Today, the percentage of respiratory diseases in the global mortality rate remains significant. For example, COPD, a disease with a pronounced obstructive syndrome, is the third most frequent cause of death in the world. Pathologies of this kind can be diagnosed using various methods, but the simplest and most accessible one is spirometry with the flow-volume curve tracked. Spirometry is based on comparing the obtained values of the patient's respiratory function with the predicted values calculated according to a given system. This approach has been used in clinical practice for a long time, and has often been criticised. It may be beneficial to consider using new indicators or methods for clarification of the conclusions based on the flow-volume curve. The present study of diagnostic efficiency of flow-curve evaluation based on changes in its shape in patients with obstructive disorders allows us to consider them as highly accurate methods of diagnostics of obstructive processes in bronchi (in particular, the methods of assessing the angle β and the total concavity of the flowvolume curve with the mean diagnostic sensitivity of 87.8% and 95.6%, respectively). In contrast, the AEX-FV assessment has high mean specificity (88.6%), suggesting that it is more oriented towards preventative screening of obstructive type respiratory disorders. However, these methods should not be used in isolation from the accepted reference equations, as, in our opinion, doing so is not reasonable for clinical practice. It appears more logical to use them together to mutually improve diagnostic capabilities. It is this joint use, in our opinion, that can potentially have the greatest efficiency for practical medicine. Thus, the direction of future research in this area is identified.

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