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Spirometry: Quantification of the Shape of the Maximal Expiratory Flow-volume Curve

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The relationship between Forced Expiratory Volume in one second (FEV1) and the Forced Vital Capacity (FVC) is intensively used in diagnosing because of its quantitative description with the index FEV1/FVC. There is not such index for the relationship between airflows (Peak Expiratory Flow (PEF) and Maximal Expiratory Flow at xx% of FVC (MEFxx, where xx=75, 50, 25%)). Our aim was to describe that relationship quantitatively with the angle alfa between the 4-dimensional vector F=[PEF,MEF75,MEF50,MEF25] and the plane determined by two reference vectors: the mean of such vectors for the young and elderly. The reference vectors were found with data for 1,120 males and 1,625 females – Polish (white) population, healthy, never-smoking, aged 18–85 yrs, who performed a technically adequate spirometry maneuver. Upper Limit of Normal (ULN) was determined with the linear regression of the 5th percentiles of alfa on age (0.074*age+2.76). Such an ULN seems to well indicate both improper examination and non-healthy persons.

K e y w o r d s: spirometry, forced expiration, flow-volume curve, maximal expiratory flow

1. Introduction

Spirometry, especially the forced expiratory maneuver, is the most fundamental and frequently used method of respiratory system examination. If the expiration is really forced, the values of spirometric indexes do not depend on patient's activity. They depend only on properties of the respiratory system because of the airflow limitation phenomenon [1–3]. Therefore, if the expiration is forced, the indexes should show whether the bronchial airflow capacity corresponds to the lungs size or is too

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small, i.e. an obstruction has appeared. According to the present recommendations, the evaluation of a spirometric examination begins with the analysis of the ratio between the Forced Expiratory Volume in one second (FEV1) and the Forced Vital Capacity (FVC). FEV1 describes approximately the airflow capacity whereas FVC is connected with the lungs size. The ratio known as the FEV1/FVC index has been introduced by Tiffeneau and Pinnelli about 60 years ago [4].

Mathematically, FEV1/FVC is equal to the tangent of the angle between the vector [FVC,FEV1] and the FVC axis in the 2-dimensional space (the plane) determined by FVC and FEV1. Hence it appears that FEV1/FVC is independent of the vector length. Therefore, although it has been well known that FVC and FEV1 (and thus the vector length) depend distinctly on inter-personal differences (as sex, age, and height), it could be expected that FEV1/FVC is independent of such differences. For that reason, in the previous GOLD recommendations [5], the constant value of FEV1/FVC equal to 0.70 was assumed as the Lower Limit of Normal (LLN) to diagnose the obstruction in chronic obstructive pulmonary disease (COPD), irrespectively of the differences between examined subjects. Recent studies have shown that FEV1/FVC changes with age: it is reduced for elderly subjects [6,7]. Therefore, the present recommendations take into account the age-related alteration of the index. FEV1/FVC less than age-dependent LLN is currently the first step of obstruction diagnosing [8].

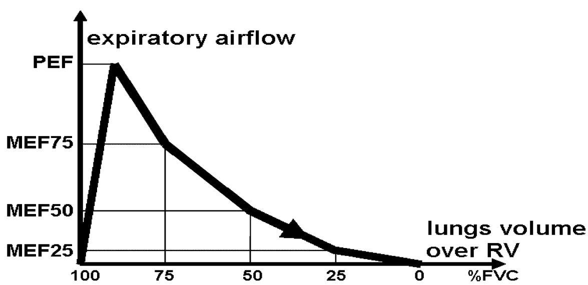

Fig.1. A schematically presented flow-volume curve. MEFxx – expiratory airflow at moment when in the lungs remains xx percent of Forced Vital Capacity (FVC)

Despite such meaning of the FEV1/FVC index, it has two significant imperfections:

– inability to indicate the obstruction that appears after the first second since FEV1 describes the volume expired only during the first second,

– inability to indicate whether a person performs a technically adequate spirometry maneuver since the volumes are the integrals of the airflow and thus cannot reflect the expiration course in time.

The two above problems may be recognized by a physician who analyses the shape of the flow-volume (F-V) curve, i.e. the expiratory airflow plotted against the expired volume (Fig. 1). However, such recognition bases only on the physician experience because there is not any index that would quantify the shape. Therefore, one physician may to diagnose early stage of COPD while another may treat the same person as healthy.

The present recommendations for COPD diagnostics are very precise and restricted, what may be the reason that they disregard obstructions in the smallest bronchi because such obstructions are not indicated by FEV1/FVC. Indeed, resistance of such bronchi rises as the lungs volume decreases, and thus even if the resistance is increased because of obstruction, it influences the airflow only at the end of the forced expiration. Therefore:

– it cannot influence FEV1 being the result of the first second of the expiration,

– its influence is visible at the F-V curve but is not taken into account during precise (quantitative) interpretation of the spirometric examination because of absence of any index that quantifies the F-V curve shape.

Taking into account that the expiratory airflow plotted against the expired volume carries the whole information about the forced expiratory maneuver, the authors suggest to quantify the F-V curve shape. The proposed index might describe how typical is the curve shape, and thus it should indicate both the maneuver adequacy lack and influence of diseases.

2. Material and Methods

2.1. Material

Military Institute of Health Services in Warsaw conducted the project "Hope for Lungs" in 2002–2005. The authors utilized the results of the project in the analysis of the relationship between PEF, MEF75, MEF50, and MEF25. The examinations were performed in 93 locations, in both large cities and villages. For all subjects in the sitting position, the examination was performed using the same spirometer (LungTEST1000 by MES Poland). The spirometer was regularly calibrated and operated by 6 qualified employees working in shifts. The results of the examinations of smokers, subjects diagnosed with COPD, those reporting the occurrence of a chronic cough or dyspnea within last 12 months, as well as individuals who were unable to undergo spirometry have been excluded from the analysis. For a technical evaluation of the examination, the following criteria was accepted: correctness (time of achievement of the peak flow tPEF<300 ms and plateau at the end of expiration – the volume expired within 1sec <25mL) and repeatability (difference of the highest values of FEV1 and FVC <150mL). 3505 females and 3596 males have been rejected due to failure to conform these criteria. Consequently, the results for 1625 from 5130 females and 1120 from 4716 males have been used in the analysis. Table 1 presents details concerning the examined population.

Table 1. Reference sample selection criteria and characteristics of the study sample

	Males	Females
Participants (n)		
Total	4716	5130
Less age outside the range	4293	4767
Less ever smokers	2385	3382
Less invalid or irreproducible data	1454	1825
Less no healthy subjects	1120	1625
Age in years (n)		
19–45	311	316
46–65	472	766
65–85	337	543
Age (yrs)	55±16	57±14
Height (cm)	173±7	161±6

Data are presented as absolute values or mean±SD. FEV1 – forced expiratory volume in one second; FVC – forced vital capacity.

2.2. The Angle Determination

It has been employed the method that was used previously for quantification of the arterial blood flow waveform [9,10]. According to that method, subjects were divided into three groups of three age ranges (age<45, 46<age<65, age>66). Subjects younger than 45 yrs were treated as 'young' whereas persons older than 66yrs created the old group. The 'group' vectors for the young and elderly were determined as follows:

– for each person, the 4-dimension vector $[x_1, x_2, x_3, x_4]$ was created with the values of PEF, MEF75, MEF50, and MEF25,

– the vector was normalized to make it independent of such inter-personal difference as height (the vector should describe the shape of the curve, not the absolute value of airflows; indeed, without the normalization, a tall person with greater lungs would have greater significance during calculation of the mean than a short one); the normalization means dividing x_i by sqrt($x_1^2 + x_2^2 + x_3^2 + x_4^2$), where sqrt is the square root,

– such vectors, separately for both groups, were added, i.e. the vectors $[x_{1a}, x_{2a}, x_{3a}, x_{4a}]$ was created, where x_{ia} is the sum of x_i from vectors for particular persons from the group a=young or a=old,

– the 'group' vectors were orthogonalized and normalized to obtain the orthonormal (Cartesian) coordinate system determining the plane of 'typical' (average) shapes of the F-V curve.

The angle *alfa* between the vector of a particular subject and the plane was calculated as the angle between the vector and its projection on the plane. Thus, *alfa* describes how much is a particular vector different from the typical vectors creating the plane. Figure 2 presents graphical interpretation of the above.

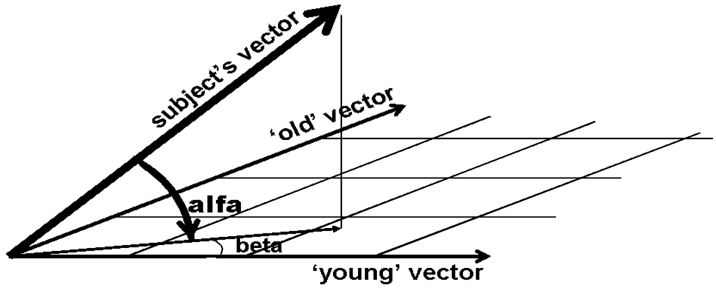

Fig. 2. The idea of quantification of flow-volume curve shape. 'Young' and 'old' vectors corresponding to the mean curve for the young and elderly determine the plane of typical vectors-curves. The vector--curve of a subject usually is not exactly typical, and thus it does not lie on the plane. The proposed index is the angle *alfa* between the vector-curve and the plane. *beta* is the angle between the 'young' vector and the projection of subject's vector on the plane

Note that the angle *beta* that is contained between the individual vector projection on the plane and the axis of the young may be treated as some kind of 'age' of the curve shape.

2.3. Upper Limit of Normal (ULN)

A result of medical examination is treated in medicine as disease indication if it is too big (or too small). The assumed limit is the probability less than 5% ($p < 0.05$) that such big (small) result could be observed for a healthy person. Therefore, the 5th percentile ULN was determined for *alfa*. Since *alfa* appeared dependent on age, the method that was proposed in [11] was applied. According to that method, the 5th percentile for each age was determined as follows:

1. The pairs of data (age, *alfa*) for particular persons were sorted in order to obtain the age-series of the pairs, i.e. the series with consecutively increasing age.
2. The sub-series of the first 100 pairs from the age-series created the first considered set.
3. The mean of the age values from 50th and 51st pairs of the sub-series was assumed as the 'age' of the set.
4. The pairs in the set was sorted in order to obtain the *alfa*-series of the 100 pairs with consecutively increasing *alfa*.
5. The mean of the *alfa* values from the 95th and 96th pair of the *alfa*-series was assumed as the 5th percentile for the age determined as above (step 3) – thus, the pair (age, 5th percentile) appeared.
6. The new set of 100 pairs was created as follows: (a) the pair with the smallest age was rejected from the set, (b) the set was supplemented with the pair that had the smallest age and has had not been considered yet.

7. If execution of the 6th step was possible, then the 3rd – 6th steps were executed again, else the above calculation was finished and the regression of the 5th percentile on age for the found pairs (age, 5th percentile) was performed to receive the formula describing ULN in relation to age.

3. Results

Figure 3 presents the dependence of *alfa* on age. The lung function probably varies more with increasing age [7], which should be manifested as smaller conformation of the F-V curve shapes. Therefore, as it can be expected, the mean of *alfa* increases with age. Despite that fact, the *alfa* values are clustered for the majority of healthy persons.

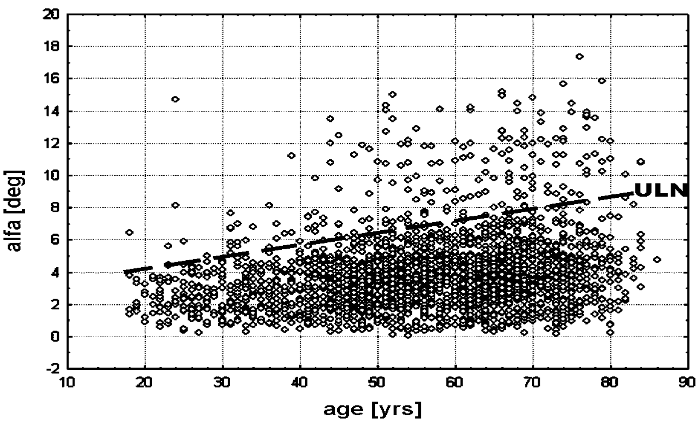

Fig. 3. The index *alfa* value plotted against age. ULN – Upper Limit of Normal

In everyday practice, it will be the most important to determine whether a shape is enough typical to be accepted as proper or the corresponding examination should be analyzed carefully. The 5th percentile LLN or ULN is commonly used in medicine for such kind of determination. In the case of *alfa*, age-dependent ULN is proposed. It can be described with the linear equation: ULN=0.074*age+2.76

4. Discussion

Even if the values of MEFxx are taken into account during diagnosing, they are considered separately. It is assumed that each of MEFxx is correct if it is greater than LLN, i.e. if the deviation of MEFxx from the predicted value (PV) for individual age and height is not too great. It would be a proper approach if the deviations of all

MEFxx were approximately equal. It would mean the normal shape. However, if some of MEFxx are smaller than their PV (but greater than LLN) and other are greater, it may suggest either unrecognized disease or unrecognized wrong performance of examination. For example, if PEF and MEF75 are equal to 90% of their PVs while MEF50 and MEF25 are equal to 125% of PVs then improper examination should be suspected (too slow expiration, i.e. deep but not forced expiration). On the other hand, if PEF and MEF75 are equal to 125% of their PVs whereas MEF50 and MEF25 are equal to 90% of PVs then obstruction in the smallest bronchi may be suspected (e.g. the first symptoms caused by smoking in an individual with big airflow capacity of the other bronchi causing big PEF and MEF75).

The above shows that the mutual relationship between all MEFxx should be analyzed as in the case of FEV1 and FVC. However, although there is the index that quantifies the relationship between FEV1 and FVC (i.e. FEV1/FVC), there is not any index quantifying the relationship between PEF, MEF75, MEF50, and MEF25. *Alfa* – the index that is proposed in the paper – seems to fill up the vacancy.

According to ATS/ERS recommendations [12], the predicted values of FEV1/FVC and its LLN have to be calculated from FEV1/FVC values obtained for individuals from an investigated population. In particular, the predicted value of FEV1/FVC cannot be calculated as the ratio of the predicted values of FEV1 and FVC. For the same reasons, 'predicted' vectors – whether they are the reference vectors or the projections of subjects' vectors on the plane – have not been determined with predicted values of PEF and MEFxx.

As FEV1/FVC is the tangent of the angle between FVC axis and vector [FVC,FEV1], it describes the direction of the vector in the 2-dimensional space. *Alfa* also describes the direction in the space. The fact that the space is a 4-dimensional space may be difficult to comprehend for non-mathematicians, however, it is not any problem for microprocessors in modern spirometers to calculate the *alfa* value for an individual. Such already calculated value could be used in diagnosing.

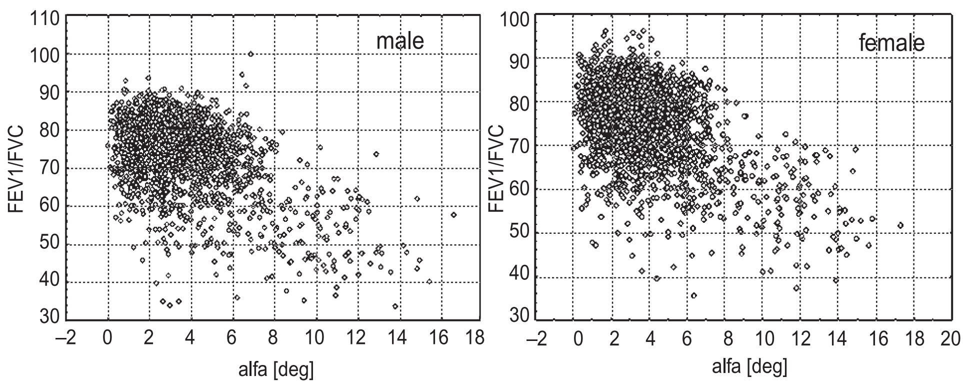

Fig. 4. The index *alfa* value plotted against FEV1/FVC. Note that the cluster consist of approximately 1000 subjects

As Figure 4 shows, data for the majority of subjects accepted as healthy persons who performed the forced expiratory maneuver adequately create a cluster. However, data for small percent of such subjects are dispersed. For example, in the case of males, a few persons have abnormally high FEV1/FVC. Since also *alfa* is relatively high, it can be supposed that the maneuver has been performed wrongly (too short expiration). There are persons – between both males and females – who have *alfa* unacceptably high (over ULN) while FEV1/FVC should be accepted according to current recommendations. Probably, these persons are suffering from unrecognized obstructive lungs' disease in the smallest bronchi. If such obstruction is more significant, FEV1/FVC is small and at the same time *alfa* is great (hence some negative correlation may be observed in Fig. 4).

As *alfa* describes how typical is a curve, the angle *beta* (Fig. 2) shows whether the curve is more similar to the 'young' curve or to the 'old' one. Since the mean 'young' curve was obtained from data for young respiratory systems (young subjects) and the 'old' one for old respiratory systems, *beta* could be treated as some measure of respiratory system ageing advance, i.e. as an index of biological age of the system. Therefore, the relatively strong interdependence between *beta* and FEV1/FVC (Fig. 5):

– confirms recent results of other authors suggesting that ageing decreases FEV1/FVC,

– shows agreement between age-related changes of different aspects of the forced expiration,

– suggests that even a significant decrease of FEV1/FVC may be connected with ageing rather than obstructive disease (some of subjects have small FEV1/FVC and *beta* typical for the middle-aged or a little older what may suggest a disease, however, another part of subjects has both small FEV1/FVC and big *beta* what suggests advanced biological age rather than a disease).

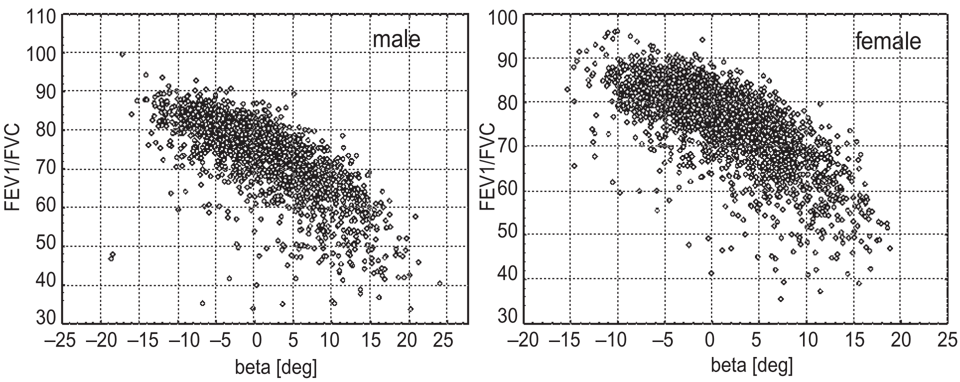

Fig. 5. The index *beta* value plotted against FEV1/FVC (in the figure, *beta* is scaled in such a way that: (a) the greater the *beta*, the older the curve, and (b) *beta*=0 means the typical curve for the middle-aged)

In the paper, *alfa* and *beta* are angles in the space of only 4 dimensions because data that would enable the authors to reconstruct the whole curve were inaccessible. It is proposed, however, to employ the airflows for all moments registered by spirometers in the final version of the index. Certainly, cooperation with a producer of spirometers is necessary to elaborate such version of the method.

5. Conclusion

As FEV1/FVC is a quantitative measure of the relationship between FEV1 and FVC, *alfa* – the index that is proposed by the authors – is a quantitative measure of the relationship between airflow values. As the airflow characterizes the expiration course, *alfa* may be especially useful in analysis whether the forced expiratory maneuver is performed correctly or not. It may be also useful in diagnosis of such diseases which do not influence FEV1, and thus cannot be indicated with FEV1/FVC.

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