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Use of Area under the Expiratory Flow-volume Curve and Rectangular Area Ratio in Detecting Ventilatory Impairments in Spirometry: A Pilot Study

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- Spirometry
- Flow-volume curve
- Rectangular area ratio (RAR)
- ventilatory impairment
- Aex ratio

Abstract

Purpose: This study aimed at demonstrating the reliability of surface area under the maximum expiratory flow volume curve (Aex) and rectangular area ratio (RAR) to define the type of ventilatory impairment and assessing potential clinical value of Aex ratio (measured / predicted Aex) to indicate the severity of ventilatory obstruction. **Methods*:*** Spirometric data of 75 subjects were analyzed by qualified pulmonologists to distinguish between different spirometric patterns representing expert decision. Computerized graphic analysis methodology was used, Aex was used to calculate other parameters (area of concavity and RAR) and an algorithm for diagnosis was proposed. For validation of the proposed grading and cutoff values, we compared them with expert decision using classification and regression trees (CART). ***Results:*** According to calculated parameters, obstructive pattern is realized if *area of concavity (Au)* has positive value and RAR is less than 0.5. While convexity/linearity is indicated if RAR $\geq$ 0.5 and *Au* has negative value or equal zero, indicating normal or restrictive pattern. Aex ratio was selected as second-best predictor of restriction at a cut-off value of 49%. Furthermore, the diagnostic performance of Aex ratio in predicting moderate-to-severe obstructive lung disease was excellent. **Conclusion:** The proposed computerized technique succeeded using RAR and Aex in differentiating between restriction, obstruction and normal patterns. Additionally, Aex ratio may be a valid parameter to grade the severity of obstruction.

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INTRODUCTION

Spirometry is the most frequently used measure of lung function. It is a valuable tool for analyzing the flow of air passing into and out of the lungs. Lung flow is graphed as a flow volume loop, in which airflow is plotted as a function of volume during inspiration and expiration [1,2]. Several parameters can be obtained or calculated from the flow volume loop graphs to give information about disease states. Changes from expected values can be used to diagnose a variety of pulmonary conditions and to follow their progress over time [1].

The most frequently used spirometric parameters derived from the maximum expiratory flow volume curve (MEFVC) for diagnosing and assessing the degree of lung function impairments are: forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), the ratio FEV_1/FVC, peak expiratory flow (PEF), forced expiratory flow at 25%, 50% and 75% of FVC ($FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, respectively) and maximum mid-expiratory flow (MMEF).

Conventional lung function parameters sometimes poorly reflect patient symptoms or are insensitive to changes, particularly in the small airways where the disease may originate or manifest [3]. Attempts have been made to derive other quantitative parameters by analyzing the MEFVC. Among these, is the value defining the surface area under the MEFVC (Aex). Aex was proposed to be a sensitive parameter for the evaluation of airway patency; after induced bronchoconstriction and bronchodilation, in comparison with conventional parameters measured from the MEFVC [4,5]. Also, measuring the Aex increases the sensitivity and predictive value of exercise challenge test, preventing under diagnosis of exercise induced bronchoconstriction [6]. Moreover, the ratio between the Aex and the predicted Aex (Aex ratio/index) has been found to differentiate between different spirometric patterns when compared with the ratio of maximum expiratory flow (MEF) to FVC (MEF/FVC) [7]. The advantage of using Aex is its ability to assess the whole area under the curve not separate points so it could be more accurate. Furthermore, it is practically easier to focus on one parameter in which several parameters are incorporated than several parameters, which decreases the probability of errors. However, studies for validation of Aex are few.

Morphology of the MEFVC is very useful for detecting the characteristic concavity, due to the slowing of expiration at low lung volumes, in obstructive patterns [1,8]. While direct visual inspection is a simple qualitative method for detecting changes in the shape of the MEFVC, it does not quantify the extent of the change and may be confusing in mild ventilatory disorders.

Some attempts [9-11] have been made to quantify the concavity in the expiratory flow-volume curve, as a marker of expiratory flow limitation. A novel parameter obtained by dividing the area under the expiratory flow-volume curve by the surrounding rectangular area; the rectangular area ratio (RAR), was found to be indicative of the concavity of the expiratory flow-volume curve in chronic obstructive pulmonary disease (COPD), considering RAR below 0.5 as an indicator of expiratory limb concavity [12-15]. However, to the best of the authors' knowledge, the clinical relevance of RAR in detecting and differentiating between different spirometric patterns (normal/ obstructive/ restrictive) has not been studied yet.

Other researchers [16] used calculus to provide an additional way of describing curve configuration. The second derivative of a function can describe its convexity or concavity. If the second derivative of a function is positive, the curve is described as "concave upward"; if it is negative, the curve is described as "concave downward."

Besides the important role of spirometry to document the presence of airway obstruction, spirometry values are used to categorize the severity of obstruction. FEV_1 as a percentage of the predicted value (FEV_1 % pred.) is the recommended parameter by the American Thoracic Society (ATS)/European Respiratory Society (ERS) as the basis for this categorization [8]. Current ATS/ERS recommendations define an FEV_1 % pred. of ≥ 70% as mild obstructive impairment, 60–69% as moderate impairment, 50–59% as moderately severe impairment, 35–49% as severe impairment, and < 35% as very severe impairment [8]. However, the use of percent predicted in this way leads to a definite age-related bias. Thus, evaluation of other alternative parameters for grading obstructive impairment may help to overcome biases related to age, height, and sex.

Using graphical analysis of the MEFVC, this study aimed at demonstrating the reliability (sensitivity, specificity) of the RAR and Aex ratio to define the type of ventilatory impairment and assessing the potential clinical value of the Aex ratio as an indicator of the degree of severity of airflow obstruction.

Methods

Study Design

This study includes:

- Physiological methodology
- Computerized graphic analysis methodology
- Statistical methodology

Physiological methodology

Baseline spirometric data of 100 subjects who attended to the Clinical Pulmonary lab, Clinical Physiology Unit, Medical Research Institute, Alexandria University, Egypt, were examined (personal data were hidden). Spirometry, including FVC measurements as well as MEFVC recording, was performed using a computerized dry spirometer (Jaeger, Germany), according to the European Respiratory Society (ERS) and American Thoracic Society (ATS) protocol for spirometry standardization [8]. The spirometric data were assessed by three qualified pulmonologists blindly and independently to distinguish between different spirometric patterns (normal/obstructive/restrictive) according to ATS guidelines [8] to represent an expert decision.

Data showing errors and mixed obstructive/restrictive cases were excluded. 25 cases were discarded. The data of the remaining 75 subjects (35 male and 40 female, aged between 20 and 60) were analyzed.

Computerized graphic analysis methodology

In this work, to assess the concavity/convexity of the MEFVC, parameters depend on the spirometric data: area under the MEFVC (Aex), peak expiratory flow (PEF) and forced vital capacity (FVC) were calculated. The calculation and the proposed diagnosis were automatically implemented through a software program built on MATLAB R2017a (Matrix Laboratory Software) [10,17,18]. A graphical user interface (GUI) is built, in which the doctors introduce the values of the needed parameters for calculation (best FVC, best PEF, actual Aex, and predicted Aex) which are all measured parameters of the used spirometer. The designed GUI is shown in figure 1.

To check the concavity of the MEFVC we draw a diagonal line, a line that connects the best PEF and the best FVC and forms a triangle area (At) as shown in figure 2.

The main idea of the proposed graphical analysis is to assess if the MEFVC is concave or convex around the diagonal line and to compare the area under this curve by the triangle area At, where At represents the area under the ideal linear case.

The first calculated parameter is the area of concavity defined by Au. Au reflects the concavity of the curve and represents the lighted area below the imaginary diagonal line and above the MEFVC as shown in figure 2. Using the illustrated graph in figure 2, the Au was calculated as follows:

Aex = A1 + A2

A1= Aex - A2

Area of the triangle *(At) = Au + A1*

Au = At - A1= At - (Aex-A2)……… (1)

From the measured value on the graph and spirometer output parameters, we can get At.

At = 1/2*PEF*(FVC-Xp)……….. (2)

Where Xp denotes the lung volume at PEF. For simplicity, we approximate A2 to be an area of a triangle.

A2 = 1/2*PEF*Xp……….. (3)

Substitute equations (2), (3) in equation (1)

Au = (1/2*PEF*FVC) - Aex

The second calculated parameter used to measure the convexity/concavity of the curve is RAR as shown in figure 3.

Two critical points are used: the best PEF and the point at which the expiratory flow takes a sharp decline (best FVC) signaling the beginning of inspiration. We calculated the area of the rectangle (Arec) with the 2 points as vertices, where:

Arec = PEF(FVC-Xp)*

RAR = (A1/ Arec) *100%

Where *A1= Aex - A2*, Aex is an output parameter of the spirometry, A2 is obtained from equation (3).

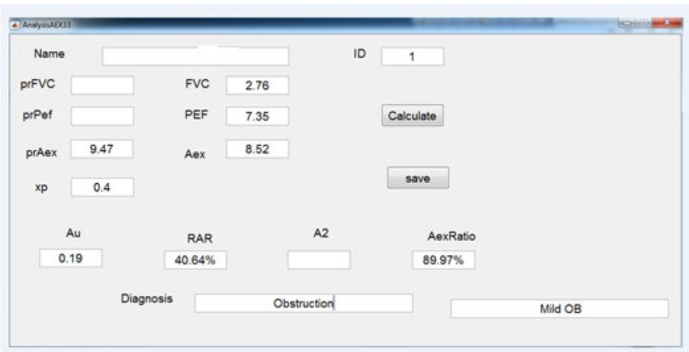

Figure (1): The graphical interface in the proposed technique. FVC, forced vital capacity; PEF, peak expiratory flow; Aex, surface area under the maximum expiratory flow volume curve; prAex, predicted Aex; Xp, denotes the expired volume at PEF; Au, denotes the area of concavity below an imaginary diagonal line and above the maximum expiratory flow volume curve; RAR, rectangular area ratio; Aex ratio, measured/predicted Aex.

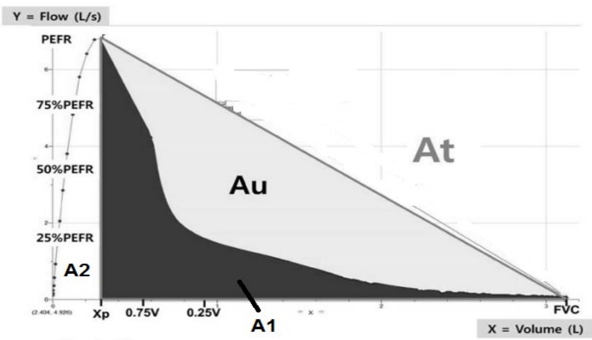

Figure (2): Graphical explanation of Au (modified from reference 14). Au, the lighted area below the imaginary diagonal line and above the maximum expiratory flow volume curve; At, the area of triangle; PEFR, peak expiratory flow rate; Xp, denotes the expired volume at PEFR; FVC, forced vital capacity; A1+ A2= Aex (surface area under the maximum expiratory flow volume curve); Au= At- A1

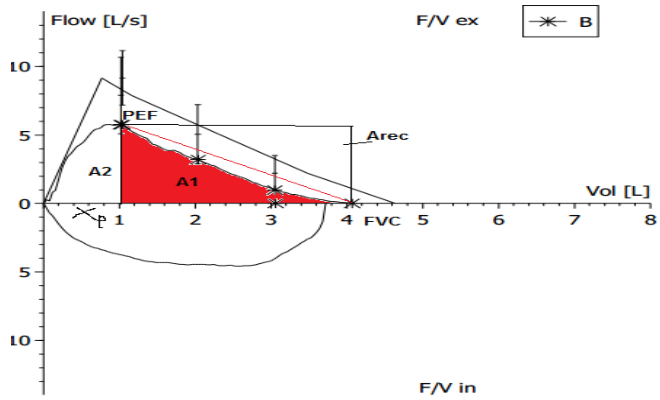

Figure (3): Method of calculation of the rectangular area ratio (RAR). PEFR, peak expiratory flow rate; FVC, forced vital capacity; Xp, denotes the expired volume at PEFR; A1+ A2= Aex (surface area under the maximum expiratory flow volume curve); Arec, area of the rectangle.

A1 represents the area formed by the curvature of the MEFVC below/above diagonal of the assumed rectangle, where in the ideal linear case it represents half the rectangular area. Therefore, the presence of curvature around the diagonal of the rectangle will affect the ratio of A1 with respect to Arec (RAR). As a result, from RAR we can estimate the convexity or concavity of the MEFVC.

The MATLAB program calculated the Au and RAR, checked their values, tested the Aex ratio and then differentiated between the different spirometric patterns according to proposed cut-off values (showed in the results). The proposed algorithm for the computerized diagnosis of the type of spirometric pattern and grading of the severity of obstructive impairment is presented in figure 4.

For validation of the proposed cutoff values, we used the classification and regression trees (CART) [19]. Where, CART is a statistical program used to determine the optimal cut-off values for continuous variables.

Statistical methodology

Qualitative data were described using numbers and percentages. The assumption of normality was tested using the Kolmogorov–Smirnov test. Continuous data were described using mean (M) and standard deviation (SD) or median (Mdn) and interquartile range (IQR). Mann-Whitney test was used to compare continuous predictors between two groups. If there are more than 2 groups, Independent one-way ANOVA test or Kruskal-Wallis test was used. The diagnostic performance was evaluated using area under the curve (AUC) of receiver operating characteristic (ROC), sensitivity (sn), specificity (sp), positive predictive value (PPV) and negative predictive value (NPV). Significance of the test results quoted as two-tailed probabilities and judged at the 5% level.

Classification and regression trees (CART) procedure creates a tree-based classification model. It classifies cases into groups based on the values of independent variables (predictors). We used decision tree to determine the optimal cut-off values for continuous variables**.** The end product of decision CART is a dendogram (a tree-like structure) that starts with a “root node” that contains the observations from which the tree will be grown. The observations are then partitioned into two “child nodes” -each containing a subset of the observations- according to the value of one of the predictors. Each child node may be further divided, again according to the value of one of the predictors. The final child nodes are named terminal nodes and they form a complete partition of the observations in the root node. The model was built in two consecutive steps. The first one aimed at predicting obstructive lung diseases among the whole sample. The second step aimed at predicting restrictive lung disease. “rpart,” a statistical R package [a], was used to conduct CART. MedCalc version 15.6.1 for Windows and SPSS® Statistics 25 was used to conduct the other statistical tests (figure 5).

Results

According to the pulmonologists' decision (based on ATS guidelines) the study sample (n=75) included: 25 obstructive, 16 restrictive and 34 normal spirometric patterns. The obstructive patterns were classified according to FEV_1 % predicted [8], into mild (n=16), moderate (n=6) and severe (n=3) obstruction. Table I compared the spirometric parameters among subjects with normal, obstructive and restrictive patterns (according to pulmonologists' decision).

A significant difference was observed among the different groups as regards all the measured parameters except PEF. Some measures (RAR, Au and FEV_1/FVC %) were significantly different ($p<0.001$ for all) in the obstructive group from both the normal and restrictive group, and some measures (*Aex* ratio, FEV_1 and FVC) were significantly higher ($p<0.001$ for all) in normal group when compared to obstructive and restrictive groups.

From the computerized graphic analysis, if the calculated Au ≤ 0 (0 or negative value), meaning that the *Aex* is equal or larger than the studied triangle area, this indicates that the MEFVC has a linear or convex shape, respectively around the imaginary diagonal line. If Au > 0 (positive value), meaning that *Aex* is less than the area of the triangle, this signifies that the curve has a concave shape below the imaginary diagonal line. So according to the sign of Au we can decide the concavity or convexity/linearity of MEFVC. Where the concavity reveals the presence of obstruction and convexity/linearity indicates restriction or normal pattern.

If RAR < 0.5, this signifies concavity as the alignment of MEFVC is below the linear diagonal of the rectangle, while RAR ≥ 0.5 represents convexity or linearity of the curve.

Thus, according to the calculated parameters, the concavity of the MEFVC, which indicates the presence of airflow obstruction, is realized if *Au* has a positive value and RAR is less than 0.5. While convexity/linearity of the curve, which indicates restriction or normal pattern, is indicated if *Au* has a negative value or equal zero and RAR ≥ 0.5.

To distinguish normal patterns from restrictive, the Aex ratio was tested after deciding the convexity/linearity of MEFVC. *Aex ratio = actual Aex / predicted Aex,* one of the measured values of spirometry. In the restrictive pattern, the restriction limits lung expansion, which affects the *Aex* in comparison with the normal pattern. Aex ratio < 48% (in convex or linear curve) was proposed to indicate restrictive impairment (considering the pulmonologists' decision).

Furthermore, for grading the obstruction severity, we worked on the *Aex* ratio after deciding that the curve is concave. In case of obstruction patient, where RAR < 0.5 and *Au* has positive value, the following severity grading was proposed (considering the pulmonologists' decision); If Aex ratio $\leq$ 30%, the obstruction is severe, if Aex ratio > 30% but $\leq$ 39.5%, the obstruction is moderate, if Aex ratio is > 39.5%, the obstruction is mild.

Thus, according to the upper explained approach and the proposed cut-off values illustrated in figure 4, the MATLAB program determined the spirometric pattern and the severity grading of obstructive patterns and display it as shown in figure 1.

Furthermore, on applying CART to determine the optimal cut-off values, it validated the results deduced by MATLAB graphical analysis. The final dendogram is shown in figure 5. Using CART, the study sample (root node) was classified according to RAR into two nodes; node 2 and node 3. Node 2 contains cases with RAR < 0.5. It contained 25 cases, most of them (n=24, 96%) had obstructive lung disease, according to the expert decision. Using RAR to predict obstructive lung disease at a cut-off value of 0.5 shows high Sn and Sp (Sn=96%, 95%CI: 77.7% to 99.8% and Sp=98% (95%CI: 88.0% to 99.9%). The probability of obstructive lung disease (PPV) was 96% (95%CI: 77.7% to 99.8%) if RAR < 0.5 and dropped to 2% (95%CI: 1% to 12%) if RAR ≥ 0.5.

Node 3 contained 50 cases with RAR ≥ 0.5. According to experts' decision, 33 of them were normal (66%), 16 were restrictive (32%) and 1 obstructive case (2%). CART was re-used to predict restrictive lung disease among node 3 cases. Aex ratio was selected as the second-best predictor of restriction (after FVC % pred.), at a cut-off value of 49%. The Sn and Sp at this cut-off value were 81.2% (95%CI: 53.7% to 95%) and 97.1% (95%CI: 83% to 99.9%), respectively. The probability of restrictive lung disease (PPV) was 87.5% (95%CI: 60.4% to 97.8%) if Aex ratio < 49% and dropped to zero% (95%CI: 0% to 12%) if Aex ratio ≥ 49%.

Use of Aex ratio for detecting the obstructive severity

The median Aex ratio among cases with moderate to severe obstructive lung disease (Mdn=0.29, IQR=0.26) was significantly (U=3.9, p<0.001) lower than mild cases (Mdn=0.52, IQR=0.14). Using ROC, the diagnostic performance of Aex ratio in predicting moderate-to-severe obstructive lung disease was excellent (AUC= 0.98; 95%CI=0.94 to 1.00, p<0.001). The proposed grading, using the Aex ratio, was validated by CART. CART determined a cut-off value of less than 39%. If the Aex ratio < 39%, the probability of moderate to severe obstruction is 81.8% (95%CI: 47.8% to 96.8%). This probability dropped to zero % (95%CI: 0% to 26.8%) if Aex ratio ≥ 39%.

The CART results confirmed the concept of the proposed computerized algorithm in:

- Applying RAR (rectangular area ratio) as a good single parameter in distinguishing between different ventilatory impairments (normal/obstructive/restrictive) and the cut-off value of 0.5 is the right value.
- Using Aex ratio (actual Aex / predicted Aex) for grading the severity of obstruction and almost used the same proposed cut-off values.
- Assuring that Aex ratio is a useful index to discriminate between normal and restrictive patterns and CART applied almost the same threshold as the proposed computerized technique.
- The overall accuracy of the proposed computerized technique was 93%; with 70 out of 75 patients were correctly classified.
    - Among patients with obstructive lung disease, 96% (24/25) were correctly classified, the remaining case was misdiagnosed as normal.
    - Similar accuracy was observed among normal cases where 97% (33/34) were correctly classified with one case misclassified as obstructive.
    - The least accuracy was observed among patients with restrictive lung disease, where 81% (13 out of 16) were correctly classified and 3 cases were misclassified as normal.

Table I Spirometric parameters among study subjects with normal, restrictive and obstructive patterns

Spirometric parameter	Normal (n=34)	Restrictive (n=16)	Obstructive (n=25)	p_1	p_2	p_3
$FEF_{75\%}$(% pred.); *Mdn (IQR)*	96.00 (28.00)	81.00 (32.50)	44.50 (30.50)	<.05	<.05	<.05
FVC (% pred.); *M (SD)*	94.26 (12.72)	57.61 (12.02)	78.25 (17.80)	<.05	<.05	<.05
FEV_1 (% pred.); *Mdn (IQR)*	99.40 (18.90)	70.70 (20.70)	73.75 (14.20)	<.05	<.05	<.05
MMEF (% pred.); *M (SD)*	98.50 (23.63)	74.33 (24.33)	47.44 (16.74)	<.05	<.05	<.05
RAR; *M (SD)*	.64 (0.09)	.62 (0.08)	.42 (0.08)	>.05	<.05	<.05
Au; *Mdn (IQR)*	-.24 (0.25)	-.21 (0.44)	.15 (0.24)	>.05	<.05	<.05
FEV_1/FVC (%); *Mdn (IQR)*	91.81 (7.06)	94.35 (9.92)	79.69 (14.94)	>.05	<.05	<.05
Aex ratio; *Mdn (IQR)*	.66 (0.33)	.41 (0.21)	.43 (0.24)	<.05	<.05	>.05
FEV_1(L); *Mdn (IQR)*	2.85 (0.89)	1.98 (1.58)	2.16 (0.71)	<.05	<.05	>.05
FVC(L); *Mdn (IQR)*	3.13 (1.37)	2.08 (1.60)	2.68 (0.50)	<.05	<.05	>.05
PEF (L/sec); *M (SD)*	5.93 (1.68)	4.85 (2.35)	4.93 (1.45)	>.05	>.05	>.05

M, Mean; *Mdn, Median; IQR, interquartile range; SD, standard deviation;* $FEF_{75\%}$, forced expiratory flow at 75% of forced vital capacity; pred., predicted; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; MMEF, maximum mid expiratory flow; RAR, rectangular area ratio; Au, denotes the area of concavity below an imaginary diagonal line and above the maximum expiratory flow volume curve; Aex, area under expiratory flow volume curve; Aex ratio, measured/predicted Aex; PEF, peak expiratory flow; p_1, p_2 and p_3, p-values for pairwise comparisons of normal vs. restrictive, normal vs. obstructive and restrictive vs. obstructive, respectively.

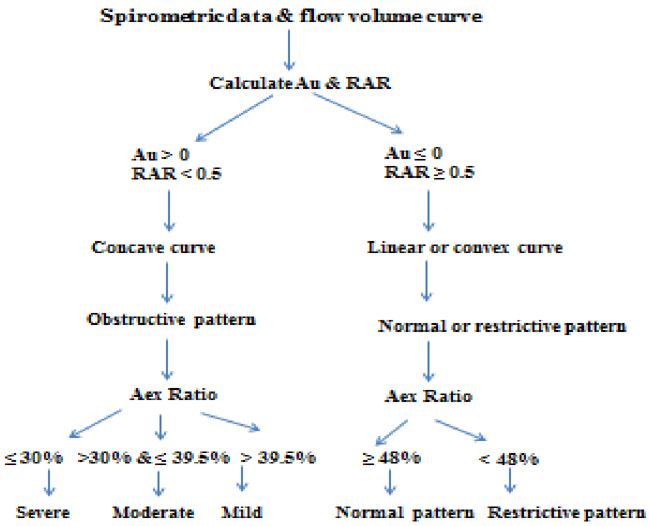

Figure (4): The proposed algorithm for the computerized diagnosis of the type of spirometric pattern and grading of the severity of obstructive impairment. RAR, rectangular area ratio; Aex ratio, measured/predicted Aex; Au, denotes the area of concavity below an imaginary diagonal line and above the maximum expiratory flow volume curve.

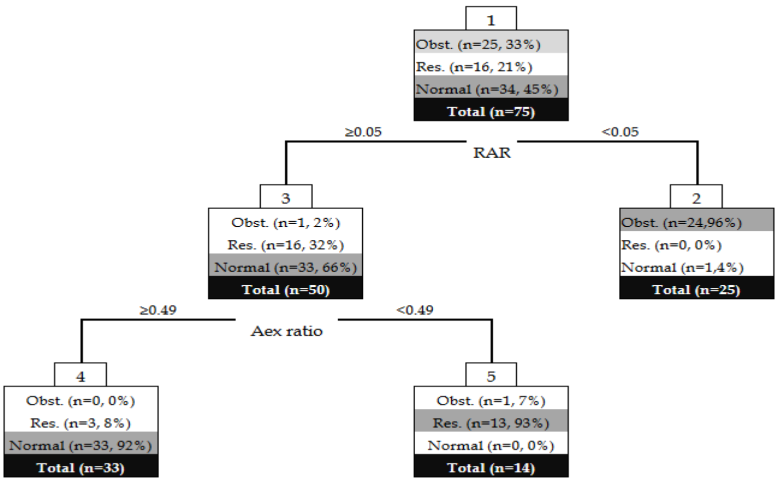

Figure (5): The dendogram produced by CART to predict the type of ventilatory impairment from rectangular area ratio (RAR) and Aex ratio (measured/predicted Aex). Node 1 is the root node, containing the whole study sample (n=75) with 33% of them with obstructive lung disease and 21% with restrictive lung disease. It was split into two child nodes according to the RAR, nodes 2 and 3. Node 3 was further split according to the Aex ratio. The terminal nodes are nodes 2, 4, and 5. Normal cases were confined to node 4, cases with obstructive lung disease were confined to node 2 and cases with restrictive lung disease were confined to node 5.

Discussion

It is well known that the pattern of the MEFVC reflects the type of ventilatory impairment [1,8]. This study demonstrates a new quantitative and objective approach that allows the differentiation between the different patterns of the MEFVC (normal/obstructive/ restrictive) using both RAR and Aex ratio. Besides, Aex ratio was found to be a useful index to predict the degree of severity of airflow obstruction.

Interpretation of spirometry may hold a challenge, as in the presence of concomitantly decreased FEV_1 and FVC with normal or near-normal FEV_1/FVC ratios [7]. This may explain the need for alternative measurements that aid in interpreting spirometry. Parameters that help to describe and quantify the configuration of the MEFVC have been suggested, such as the “area under the maximal expiratory flow volume curve” (Aex) [6].

Aex has been previously introduced to be a sensitive parameter in evaluating airway patency, using the absolute value of the Aex [4,5] and in differentiating spirometric patterns, using the Aex ratio [7]. Moreover, it has been shown to be more suitable for the evaluation of bronchial hyper-reactivity and bronchodilation than the FEV_1 [4,6]. The advantage of using the Aex in evaluating the MEFVC is that it analyzes the entire curve from the start to the end of the maneuver in segments [total lung capacity (TLC) to PEF, PEF to $FEF_{25\%}$, $FEF_{25\%}$ to $FEF_{50\%}$, $FEF_{50\%}$ to $FEF_{75\%}$, and $FEF_{75\%}$ to residual volume (RV)], as well as being sensitive to changes in the shape of the curve [20].

The present study considered using Aex in the calculation of other parameters that detect and quantify the concavity/convexity of the MEFVC; therefore, allow differentiating between the different spirometric patterns.

In the current study, via computerized graphical analysis, the concavity/convexity of the MEFVC was assessed using 2 parameters; Au and RAR, which were derived from the Aex value. The MATLAB program calculated the Au and RAR, checked their values, tested the Aex ratio and then differentiated between the different spirometric patterns according to proposed cut-off values. The concavity of the curve was reflected by a positive value of Au and a RAR value < 0.5, while zero or negative Au value and a RAR value ≥ 0.5 reflected convex or linear curves.

In support, using CART in the current work showed that RAR predicted obstructive lung diseases at a cut-off value of 0.5 with high sensitivity and specificity (PPV was 96% if RAR < 0.5 and dropped to 2% if RAR ≥ 0.5). RAR < 0.5 signifies concavity as the alignment of MEFVC is below the linear diagonal of the rectangle, while RAR ≥ 0.5 represents convexity or linearity of the curve indicating restrictive or normal pattern. However, in the current work, RAR was not useful in differentiating restriction from normal pattern. Our findings agree with other studies [12-15] that considered RAR < 0.5 as an indicator of the concavity of the curve, for assessment of flow limitation in COPD patients.

Other parameters reflecting the concavity of the MEFVC were previously derived, but their correlation with clinical and functional indices was not further investigated. Mead [21] first developed the slope ratio as an index of the MEFVC curvature, but it measures the degree of curvilinearity at a given expiratory volume only, so it was regarded as impractical to use. Zheng et al. [22] calculated a curvilinearity index using another slope parameter that measures how fast the airflow resistance increases with the expiratory lung volume, but it has a disadvantage that correct estimation of this parameter requires precise identification of the starting position of the expiratory volume (at which the flow rate=0).

The concave shape of the MEFVC reflects the slowing of the expiratory flow [8] and correlates with symptoms of airflow obstruction [23]. In the early stage of COPD, the shape of the MEFVC changes even without significant alterations in FEV_1 or FEV_1/FVC. As the obstructive disease worsens, the concave shape becomes more obvious [8]. Also, the concave shape of the curve was found to become less bowed after steroid treatment in asthma patients [24]. A relationship between the severity of obstruction and the concavity of the MEFVC was suggested [9,25].

In the present work, we assessed the potential value of the Aex ratio in quantifying the severity of airflow obstruction. Aex ratio was significantly lower in the moderate and severe obstruction than in mild obstruction ($p < 0.001$). Using ROC, the diagnostic performance of Aex ratio in predicting moderate-to-severe obstructive lung diseases was excellent (AUC= 0.98; 95%CI= 0.94 to 1.00, $p < 0.001$). CART determined a cut-off value of less than 39% to predict moderate or severe obstruction (PPV=81.8% and dropped to zero if Aex ratio ≥ 39%). This implies that the Aex ratio might be a useful parameter to quantify the severity of obstruction. However, CART couldn't validate our proposed cut-off value that differentiates between moderate and severe obstructive patterns (Aex ratio ≤ 30% in the concave curves was proposed to indicate severe obstruction), as their actual number in our sample was small (6 moderate and 3 severe obstructive patterns). A larger sample is needed for validating our proposed cut-off value.

In the present study, Aex ratio was also tested for its capacity to distinguish between normal and restrictive patterns of the MEFVC, among the linear or convex curve (zero or negative Au value and a RAR value ≥ 0.5). Aex ratio < 48% was proposed to indicate restrictive patterns. In close agreement, when CART was further applied to predict restrictive lung diseases, Aex ratio was selected as the second best predictor (after the FVC % pred.) at a cut-off value of 49% (PPV= 87.5% if Aex ratio < 49% and dropped to zero% if Aex ratio ≥ 49%). To the best of the authors' knowledge, no previous work depending on both Aex and the curvilinearity of the MEFVC has been used for detecting restrictive dysfunction.

To summarize, despite that previous researches suggested using Aex as a sensitive parameter in evaluating airway patency, they did not specify cut-off values for Aex to use. In this paper, we applied the Aex concept and defined cut-off values for Aex ratio and RAR (another parameter derived from Aex) to distinguish between different ventilatory impairments. Furthermore, we validated the proposed cut-off values by using CART.

Conclusion

The current study was capable to differentiate between the different patterns of the MEFVC, when RAR and Aex ratio were tested together. The proposed computerized technique succeeded using RAR and Aex ratio in the differentiation between normal, obstructive and restrictive spirometric patterns. Additionally, Aex ratio may be a valid parameter to grade the severity of airflow obstruction. One of the main advantages of this research is that it proposed cut-off values for Aex-derived parameters to be used as differentiation parameters between various ventilatory impairments and validated these cut-off values by using CART.

In the proposed design, doctors deal only with the proposed designed graphical interface to enter the parameter, and by one click they get an automatic diagnosis without dealing with any technical information. The proposed technique can be used for the training of young physicians as it can distinguish between common pulmonary dysfunctions. Further studies are warranted to validate the proposed diagnostic approach in a larger study sample, also to apply different classifier techniques to train the computer for automatic diagnosis.

Abbreviations: Aex, area under the maximum expiratory flow volume curve; Arec, area of rectangle; At, area of triangle; ATS, American Thoracic Society; CART, classification and regression trees; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV_1, forced expiratory volume in one second; $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, forced expiratory flow at 25%, 50% and 75% of forced vital capacity respectively; FVC, forced vital capacity; GUI, graphical user interface; MATLAB, Matrix Laboratory Software; MEFVC, maximum expiratory flow volume curve; MMEF, maximum mid-expiratory flow; PEF, peak expiratory flow; RAR, rectangular area ratio; ROC, receiver operating characteristic; RV, residual volume; TLC, total lung capacity.

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