Area under the expiratory flow–volume curve (AEX): actual versus approximated values

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ABSTRACT

Previous work has shown that area under the expiratory flow–volume curve (AEX) performs well in diagnosing and stratifying respiratory physiologic impairment, thereby lessening the need to measure lung volumes. Extending this prior work, the current study assesses the accuracy and utility of several geometric approximations of AEX based on standard instantaneous flows. These approximations can be used in spirometry interpretation when actual AEX measurements are not available. We analysed 15 308 spirometry tests performed on subjects who underwent same-day lung volume assessments in the Pulmonary Function Laboratory. Diagnostic performance of four AEX approximations ($AEX_{1–4}$) was compared with that of actual AEX. All four computations included forced vital capacity (FVC) and various instantaneous flows: AEX_1 was derived from peak expiratoryflow (PEF); AEX_2 from PEF and forced expiratoryflow at 50% FVC (FEF_{50}); AEX_3 from FVC, PEF, FEF at 25% FVC (FEF_{25}) and at 75% FVC (FEF_{75}), while AEX_4 was computed from all four flows, PEF, FEF_{25}, FEF_{50} and FEF_{75}. Mean AEX, AEX_1, AEX_2, AEX_3 and AEX_4 were 6.6, 8.3, 6.7, 6.3 and 6.1 L^2/s, respectively. All four approximations had strong correlations with AEX, that is, 0.95–0.99. Differences were the smallest for AEX–AEX_4, with a mean of 0.52 (95% CI 0.51 to 0.54) and a SD of 0.75 (95% CI 0.74 to 0.76) L^2/s. In the absence of AEX and in addition to the usual spirometric variables used for assessing functional impairments, parameters such as AEX_4 can provide reasonable approximations of AEX and become useful new tools in future interpretative strategies.

Significance of this study

What is already known about this subject?

- Usual pulmonary function testing consists of spirometry and several, more advanced lung volume assessments, such as body plethysmography, gas dilution or diffusion measurements.
- Area under expiratory flow–volume loop (AEX) is a spirometric measurement computed as the integral function of respiratory flow versus volume during a forced exhalation maneuver.
- We have shown before that the AEX has good discriminating capacity between different functional impairments and patterns (eg, obstruction, restriction, mixed defects and small airway disease) and may lessen the need to use lung volume testing.
- Only a minority of pulmonary function testing platforms compute and make available AEX measurements.

What are the new findings?

- We derived four different AEX approximations, AEX_1 to AEX_4, and compared them with the actual AEX.
- AEX approximations based on instantaneous flows at different volumes are good surrogate measurements of AEX.
- The AEX_4, derived from four instantaneous flows measured during spirometry, seems to be a good approximation or surrogate measurement for AEX.

How might these results change the focus of research or clinical practice?

- Whenever AEX is not available, the use of AEX_4 could provide additional value in the diagnosis and the severity stratification of respiratory function impairment.
- The use of such measurements could avoid the need to use more laborious, complex and expensive methods of respiratory function assessment.

INTRODUCTION

Central to spirometry interpretation is the process of comparing measured flows and volumes with reference values obtained from predictive equations that are derived from healthy subjects from similar, relevant populations.[1–3] Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC ratio and 'mid' or 'distal' flows represent the main parameters used to investigate the presence and severity of lung function impairment by spirometry. Measurements for total lung capacity, residual volume and functional residual capacity are the gold standards of pulmonary function testing (PFT) for diagnosing hyperinflation with air trapping, thoracic overdistension or restriction. Yet, these measurements add to the testing burden and may be technically challenging, thus limiting their use in clinical practice. Nevertheless, in specific clinical situations, the availability of these measurements becomes essential for unequivocal diagnosis of a

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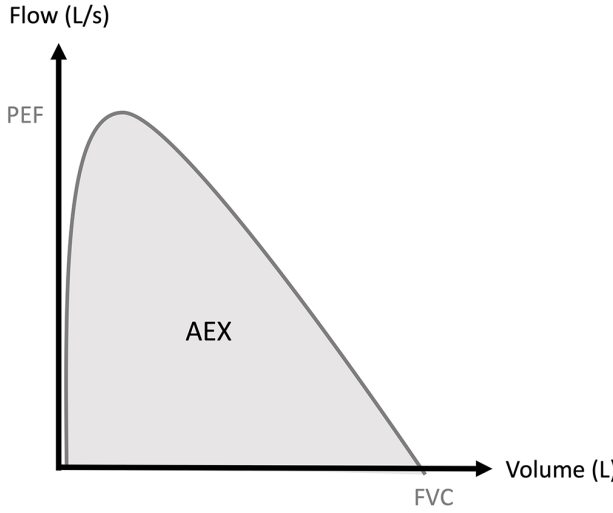

Figure 1 Area under expiratory flow–volume curve (AEX). PEF, peak expiratory flow.

physiological state or impairment.[4] Furthermore, predicted 'mid' and 'distal' flows tend to have wide CIs, limiting their diagnostic utility.

Previous work described the diagnostic utility of a novel spirometric parameter called area under expiratory flow–volume curve (AEX) (Ioachimescu OC, An alternative spirometric measurement: area under the expiratory flow-volume curve (AEX). Unpublished data, 2019).[5] as an alternative measure for categorizing and estimating the severity of PFT impairments, thereby lessening the need to assess lung volumes in a large percentage of subjects. The AEX is the actual integral function of the variable flow (on the Y axis) versus expiratory volume (on the X axis) during a forced exhalation maneuver from TLC (figure 1). AEX is expressed in L^2/s and can be computed by any PFT digital programme but appears currently to be made available on only a minority of PFT equipment manufacturers' platforms.

The current study extends our prior work by assessing the utility of several approximations of AEX derived from FVC and available instantaneous flows (AEX_1, AEX_2, AEX_3 and AEX_4; figure 2A–D). Deriving approximated values of the area under the flow–volume loop from widely available spirometric parameters may eliminate the need for actual AEX availability from the PFT equipment software, thereby extending the applicability of this novel measurement.

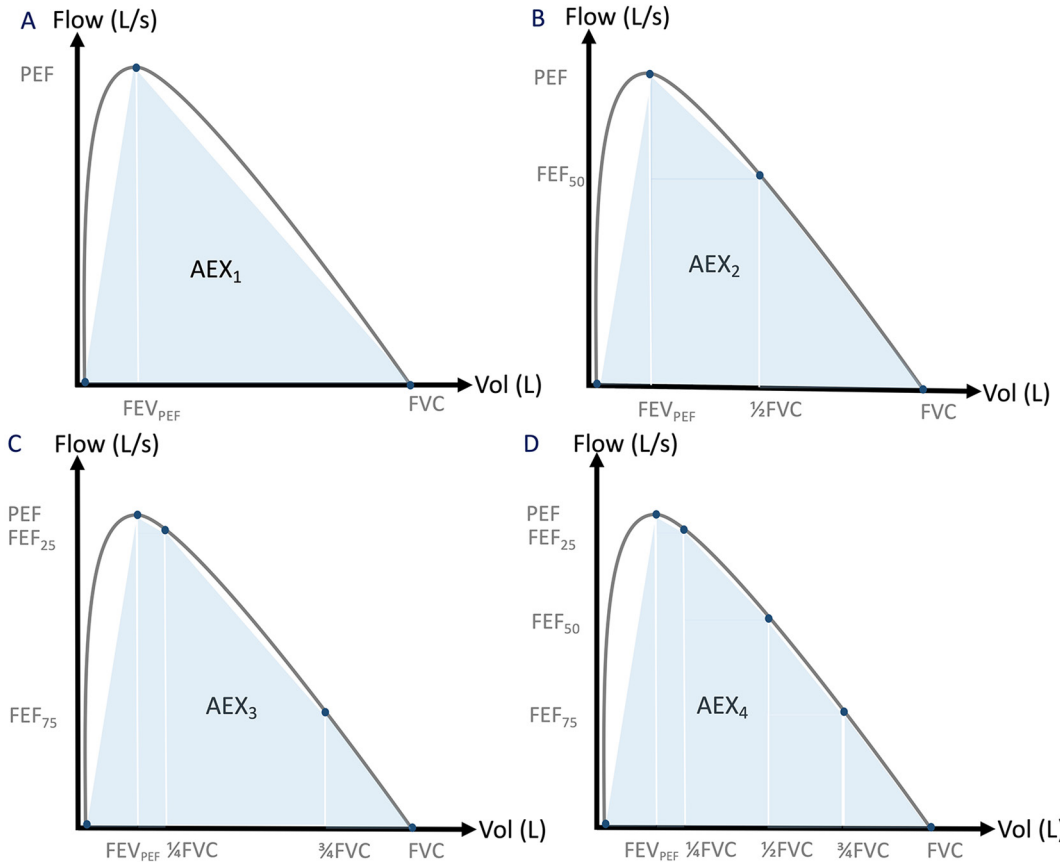

Figure 2 (A) AEX_1 approximates AEX from forced vital capacity (FVC) and one instantaneous flow: peak expiratory flow (PEF). (B) AEX_2 approximates AEX from FVC and two instantaneous flows: PEF and forced expiratory flow at 50% FVC (FEF_{50}). (C) AEX_3 approximates AEX using FVC and three instantaneous flows: PEF, forced expiratory flow at 25% and at 75% FVC (FEF_{25}, and FEF_{75}, respectively). (D) AEX_4 approximates AEX using FVC and four instantaneous flows: PEF, forced expiratory flow at 25%, 50% and 75% FVC (FEF_{25}, FEF_{50} and FEF_{75}, respectively). AEX, area under the expiratory flow–volume curve.

METHODS

The analysis was performed on a subcohort of a dataset of 21 253 consecutive prebronchodilator spirometry tests done in the Cleveland Clinic Pulmonary Function Laboratory[5] on 9328 distinct adult patients who underwent same-day lung volume determinations by either body plethysmography[6–8] or helium dilution.[9 10] Eligible subjects were adults >18 years. The AEX values were available in 15 308 tests, on which all the AEX approximations were calculated and used for analysis.

Spirometry was performed and interpreted according to the current American Thoracic Society (ATS)/European Respiratory Society (ERS) standards and recommendations.[1 11 12] Body plethysmography and helium dilution techniques were used to assess lung volumes per ATS/ERS standards and criteria.[1 4 13] Spirometry, body plethysmography and helium dilution tests were performed using a Jaeger Master Lab Pro system (Wurzberg, Germany). The most recent, comprehensive and applicable reference values, as published by the Global Lung Initiative (GLI), were used for spirometry interpretation.[2 14] For lung volumes, reference values from Crapo *et al*[15] were used. Per ATS/ERS recommendations,[13] an obstructive ventilatory defect was defined by FEV_1/FVC below the lower limit of normal (FEV_1/FVC_{LLN}) in the presence of FVC $\geq FVC_{LLN}$. Restriction was diagnosed when three criteria were satisfied: $FEV_1/FVC \geq FEV_1/FVC_{LLN}$, $FVC < FVC_{LLN}$, and $TLC < TLC_{LLN}$. If $FEV_1/FVC < FEV_1/FVC_{LLN}$, $FVC < FVC_{LLN}$ and $TLC < TLC_{LLN}$, then a diagnosis of mixed ventilatory defect was established. In this analysis, small airways disease was not assessed, as the number of subjects with all necessary flows and volumes for the computing AEX approximations was too small to be useful in the models.

We defined four spirometric variables, AEX_1 to AEX_4, that were derived from the areas of triangles and trapezoids delineated by expired volumes during the specific portions of the forced exhalation and the respective instantaneous flows. As such, AEX_1 was derived from FVC and one instantaneous flow, peak expiratory flow (PEF; figure 2A); AEX_2 was calculated from FVC and two flows, PEF and forced expiratory flow at 50% FVC (FEF_{50}; figure 2B), AEX_3 was computed from FVC and three flows: PEF, forced expiratory flow at 25% (FEF_{25}) and at 75% FVC (FEF_{75}, figure 2C); and AEX_4 was constructed from FVC and all four flows: PEF, FEF_{25}, FEF_{50} and FEF_{75} (figure 2D). Their formulas are shown here:

$$AEX_1 = (PEF * FVC)/2$$

$$\begin{aligned} AEX_2 &= [FEV_{PEF} * PEF + (PEF + FEF_{50}) \\ &*(0.5 * FVC - FEV_{PEF}) + FEF50 * 0.5 * FVC]/2 \end{aligned}$$

$$\begin{aligned} AEX_3 &= [FEV_{PEF} * PEF + (PEF + FEF_{25}) * (0.25 * FVC - FEV_{PEF}) \\ &+(FEF_{25} + FEF_{50}) * 0.5 * FVC + FEF_{75} * 0.25 * FVC]/2 \end{aligned}$$

$$\begin{aligned} AEX_4 &= [FEV_{PEF} * PEF + (PEF + FEF_{25}) \\ &*(0.25 * FVC - FEV_{PEF}) + (FEF_{25} + FEF_{50}) \\ &*0.25 * FVC + (FEF_{50} + FEF_{75}) \\ &*0.25 * FVC + FEF_{75} * 0.25FVC]/2 \end{aligned}$$

Descriptive statistical analysis of available variables was performed. Categorical variables were presented as frequencies or group percentages. Continuous variables were characterized as mean±SD (for normally distributed variables) or as median and 25th–75th IQR (for non-normal distributions). Student's t-test and analysis of variance were used to compare mean values, while categorical variables were compared using χ^2 test. The Tukey-Kramer HSD method was used to compare means among pairs when the variances were similar, while the Wilcoxon or Kruskal-Wallis rank sum tests were performed as non-parametric methods when variances were unequal, as appropriate.

Exploratory recursive decision trees were used, followed by bootstrap forest partitioning using contributory variables from the first phase. Bootstrap forest models typically fit a response value (in this case: ventilatory impairment as a categorical variable) by averaging many decision trees fitting bootstrap samples of the training data. The prediction based on the final bootstrap forest model is an average of the predicted values of the observation over all decision trees. In the end, the bootstrap forest models assessed the performance in diagnosing various spirometric patterns of several parameters: FEV_1 and FVC per cent predicted (using GLI equations), FEF_{50}*100/0.5*FVC and AEX_4. The main characteristics of these models were: 66%/33% training/validation rates, up to 10 000 trees per forest, with a minimum of 10 and maximum of 2000 splits per tree, early stopping and 21 minimum size for splits.

Statistical significance was satisfied when p values <0.05. Statistical analyses were performed using JMP Pro 14 software.

RESULTS

A total of 15 308 test sets were used to validate AEX_1, AEX_2, AEX_3 and AEX_4 (table 1). Fifty-one per cent (7822) of the subjects were men and 49% (7486) were women. Eighty-seven per cent of the tested individual were self-identified Caucasians and 13% were African-Americans. The mean age±SD was 56±14 years. The helium dilution technique was used to measure lung volumes in 40%, and body plethysmography was used in 60% of the subjects. Table 2 illustrates the main functional parameters of the test set. Using GLI predictive equations, 28%, 51%, 16% and 5% of the tests used for this analysis had normal spirometry, obstruction, restriction, or a mixed pattern.

Figure 1 illustrates the concept of AEX, while figure 2A–D shows the triangular and trapezoidal areas used for geometric reconstruction of the parameters called AEX_1 to

Table 1 Demographic characteristics of the study participants

n=15 308	Mean±SD	Median	25th–75th IQR
Race: Caucasians: 13,244 (87%); African-Americans: 2064 (13%)	–	–	
Gender: Females: 7486 (49%); Males: 7822 (51%)	–	–	
Age (years)	56±14	57	47–67
Height (cm)	168±10	168	160–175
Weight (kg)	82±21	80	67–96
Body surface area (m^2)	1.9±0.3	1.9	1.7–2.1
Body mass index (kg/m^2)	29±7	28	24–33

Table 2 Pulmonary function test measurements in the 15,308 tests

Parameter	Mean±SD	Median	25th–75th IQR
PEF (L)	5.00±2.45	4.80	3.07–6.63
FET (s)	11.12±4.02	11.79	8.02–14.90
FET_{PEF} (s)	0.09±0.06	0.08	0.05–0.11
FEV_{PEF} (L)	0.43±0.28	0.40	0.20–0.60
$FEV_{0.5}$ (L)	1.49±0.79	1.44	0.84–2.04
FEV_1 (L)	1.91±0.97	1.80	1.13–2.54
FEV_2 (L)	2.25±1.06	2.12	1.42–2.92
FEV_3 (L)	2.42±1.07	2.28	1.60–3.08
FEV_6 (L)	2.46±1.10	2.36	1.74–3.04
FVC (L)	2.87±1.09	2.75	2.06–3.53
VC (L)	2.98±1.10	2.86	2.16–3.65
FEV_1/FVC	0.66±0.20	0.72	0.51–0.82
FEV_1/FEV_6	0.66±0.17	0.71	0.52–0.80
FEF_{25} (L/s)	3.85±2.64	3.78	1.33–5.77
FEF_{50} (L/s)	2.01±1.65	1.68	0.50–3.12
FEF_{75} (L/s)	0.58±0.56	0.38	0.15–0.83
FEF_{25-75} (L/s)	1.51±1.29	1.18	0.38–2.33
FEF_{75-85} (L/s)	0.38±0.46	0.23	0.12–0.51
FEF_{50}/0.5*FVC (%)	1.37±1.12	1.17	0.41–2.01
TLC (L)	5.49±1.77	5.25	4.21–6.58
RV (L)	2.51±1.47	2.04	1.46–3.19
ERV (L)	0.83±0.51	0.75	0.45–1.11
FRC (L)	3.35±1.55	2.95	2.21–4.10
RV/TLC	0.44±0.15	0.42	0.32–0.55
IC (L)	2.15±0.85	2.05	1.53–2.65
IC/TLC	0.40±0.13	0.42	0.31–0.50

ERV, expiratory reserve volume; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; FET_{PEF}, FET at PEF; FEV_k, forced expiratory volume at k seconds of expiration; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity.

AEX_4. Figure 3 illustrates two distinct normal flow–volume curves: one in which AEX_1 is slightly smaller than the actual AEX (figure 3A), and a curve obtained in a subject with rapidly declining 'distal' expiratory flows, yet still normal, in which case the AEX_1 is larger than AEX (figure 3B). Figure 3C–E illustrate examples of possible relationships between AEX_1 and AEX in obstruction, restriction and in a subject with a mixed (obstructive–restrictive) ventilatory defect. Similar concepts are shown for AEX_2, AEX_3 and AEX_4 in figures 4A–E, 5A–E and 6A–E, respectively.

The means±SD for AEX, AEX_1, AEX_2, AEX_3 and AEX_4 were as follows: 6.6±6.1, 8.3±6.5, 6.7±5.8, 6.3±5.7 and 6.1±5.6, respectively. Figure 7 is a box-and-whisker plot showing the five variables, together with their minimal, maximal and main quartile values. Figure 8A–D includes a set of four Bland-Altman graphs that show that the smallest dispersion is achieved for the differences between AEX and AEX_4, with a mean of 0.52 (95% CI 0.51 to 0.54) and a SD of 0.75 (95% CI 0.74–0.76) L^2/s. This indicates that AEX_4 could be used with reasonable confidence (smallest dispersion) in approximating AEX. Similarly, AEX_{1-3} are potentially useful but with less accuracy than AEX_4 (higher dispersion). Figure 8A–D also shows that AEX_1 to AEX_4 tend to overestimate AEX in obstructive ventilatory defects (red markers), while in normal tests (green markers), these approximations tend to overestimate the AEX. As such, the latter finding suggests that the situations shown in figures 3B, 4B, 5B and 6B that is, 'scooping' of flow-volume curves in normal subjects, are more prevalent than the ones seen in figures 3A, 4A and 5A.

In an optimized bootstrap forest model using FEV_1 and FVC per cent predicted per GLI equations, FEF_{50}*100/0.5*FVC (a previously used ratio for diagnosing mixed ventilatory patterns[3 16]) and AEX_4, the generalized R^2, entropy R^2 and misclassification rates in the training/validation sets were 0.92/0.90, 0.78/0.73, and 11%/13%, respectively. In the validation set, the areas under receiver operating characteristic curve for normal, obstructive, restrictive, and mixed defects were 0.99, 0.96, 0.98 and 0.96, respectively. The term contributions in the model were as follows: 0.49 (FEF_{50}*100/0.5*FVC), 0.40 (FVC per cent predicted), 0.05 (FEV_1 per cent predicted), and 0.04 (AEX_4).

DISCUSSION

The main finding of this analysis is that AEX_1, AEX_2, AEX_3 and AEX_4 are useful constructs as approximations of AEX. AEX_4 most closely approximates AEX, presenting the lowest dispersion of the residual values. Like the original parameter, AEX, AEX_{1-4} are also shown to differentiate between normal lung function, obstruction, restriction, and mixed ventilatory defects. The approximated areas under the expiratory flow–volume loop (eg, AEX_4) represent alternative parameters to assess quantitatively subtle or 'distal' changes of the flow-volume curve area, especially for mixed ventilatory defects and/or small airway disease.[5 17–19] As noted before, the terminal segment of the flow–volume curve is relatively independent of effort, being the end result of the complex interplay between airway resistance to flow (especially in the small airways) and respiratory system's elastic recoil,[20] which in practice is difficult to assess quantitatively.

In this analysis, using bootstrap forest models based on FEV_1 and FVC per cent predicted by GLI equations, FEF_{50}*100/0.5*FVC (a validated ratio for diagnosing mixed ventilatory patterns) and AEX_4, the misclassification rates for mixed and restrictive ventilatory patterns were relatively low, and the contribution of AEX_4 to these models was almost as important as FEV_1 per cent predicted. In bootstrap forest models based only on FEV_1 and FVC per cent predicted and AEX_4, the AEX_4 contribution to the model went up to 11%, at the expense of the misclassification rate, which was up to 17% in the validation set.

An additional parameter, AEX_7, derived from FVC, and the flows PEF, FEF_{25}, FEF_{40}, FEF_{50}, FEF_{60}, FEF_{75} and FEF_{80} were also evaluated. While some of these instantaneous flows are generally not included in the standard reports and are not used in pulmonary function interpretation, they are easily retrievable in today's era of digital spirometry. The mean difference between AEX_7 and AEX_4 was negligible (−0.063, 95% CI −0.046 to −0.082 L^2/s) and with a very small variance of the residuals. On balance, the more precise AEX approximation called AEX_7 was quite similar to AEX_4 and contributed incrementally very little to the overall diagnostic accuracy, making the AEX_4 the best surrogate measurement as an approximation of AEX.

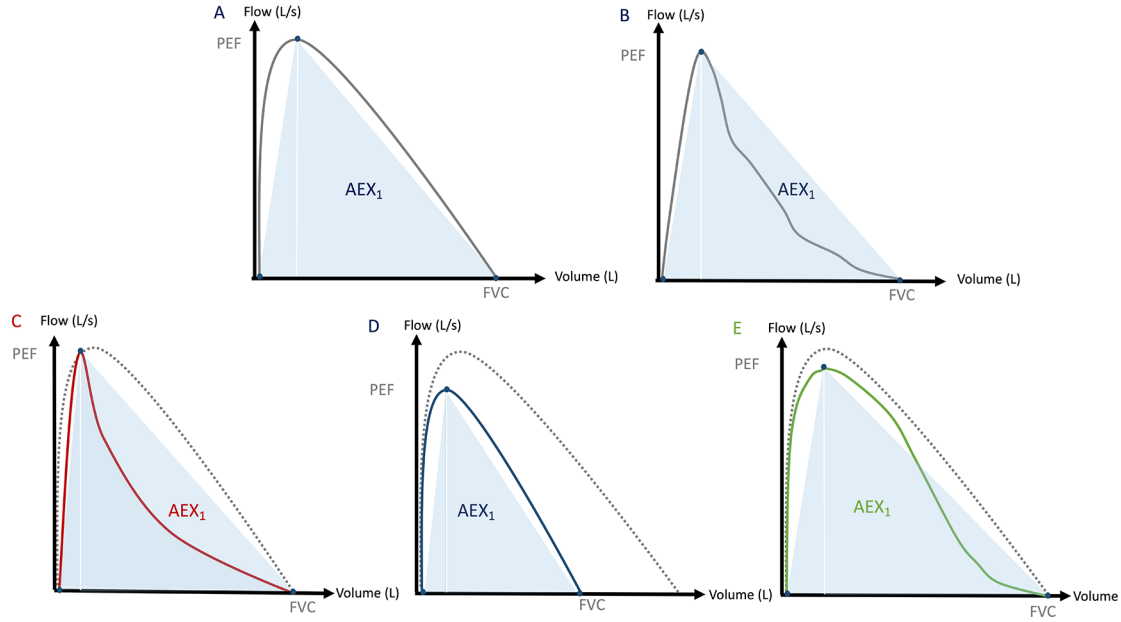

Figure 3 (A) Graphic example of AEX_1 in a normal subject in whom AEX_1 <AEX. (B) Representation of AEX_1 in a subject with normal spirometry (all flows and volumes are above lower limits of normal) and 'concave' appearance of the flow–volume curve. Here AEX_1 >AEX. (C) AEX_1 in obstruction (airflow limitation) in a subject with preserved peak expiratory flow (PEF) and forced vital capacity (FVC). Here AEX_1 >>AEX. (D) Graphic example of AEX_1 in a patient with restriction to ventilation in whom AEX_1 <AEX. (E) AEX_1 in a patient with a mild mixed pattern (obstruction and restriction), in which both overestimation and underestimation are possible. Dotted lines illustrate isovolumic predicted normal expiratory flows. Red: obstruction; blue: restriction; green: mixed ventilatory pattern. AEX, area under the expiratory flow–volume curve.

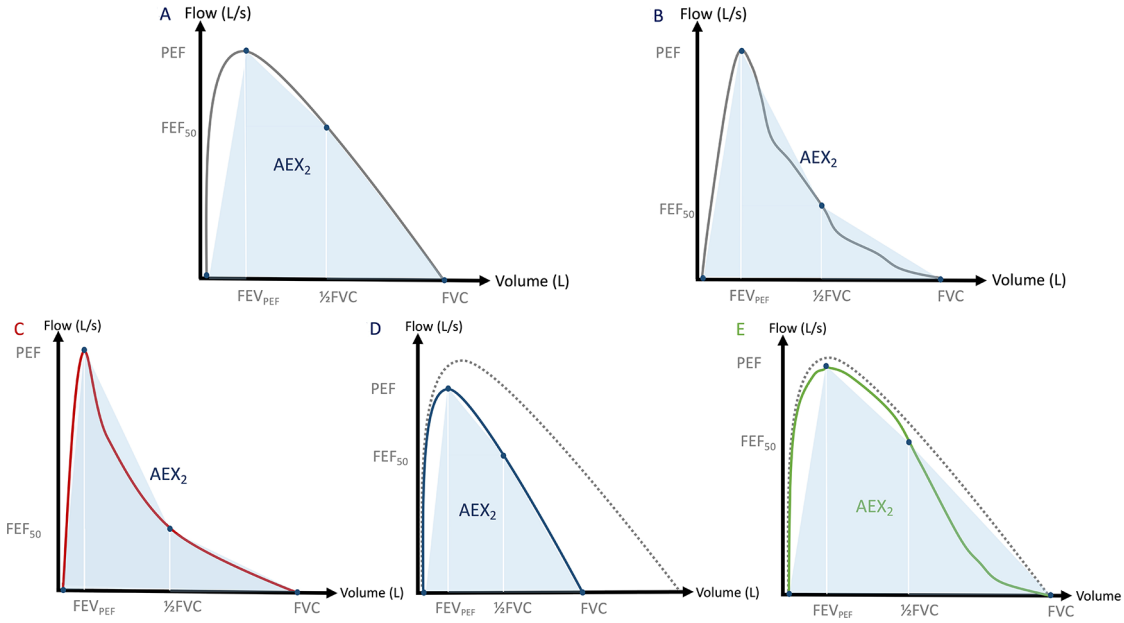

Figure 4 (A) Graphic example of AEX_2 in a normal subject in whom AEX_2 <AEX. (B) Representation of AEX_2 in a subject with normal spirometry (all flows and volumes are above lower limits of normal) and 'concave' appearance of the flow–volume curve. Here AEX_2 >AEX (overestimation due to the concavity of the curve). (C) AEX_2 in obstruction (airflow limitation) in a subject with preserved peak expiratory flow (PEF) and forced vital capacity (FVC). Here AEX_2 >>AEX. (D) Graphic example of AEX_2 in a patient with restriction to ventilation in whom AEX_2 <AEX. (E) AEX_2 in a patient with a mild mixed pattern (obstruction and restriction), in which both overestimation and underestimation are possible. Dotted lines illustrate isovolumic predicted normal expiratory flows. Red: obstruction; blue: restriction; green: mixed ventilatory pattern. AEX, area under the expiratory flow–volume curve.

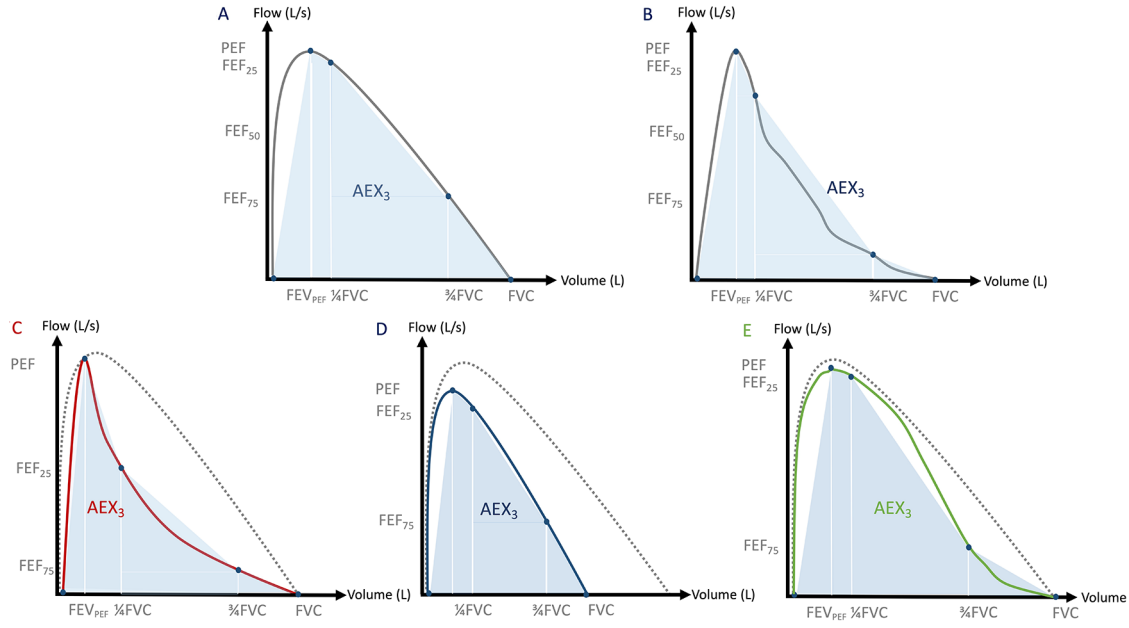

Figure 5 (A) Graphic example of AEX_3 in a normal subject in whom AEX_3 <AEX. (B) Representation of AEX_3 in a subject with normal spirometry (all flows and volumes are above lower limits of normal) and 'concave' appearance of the flow–volume curve. Here AEX_3 >AEX. (C) AEX_3 in obstruction (airflow limitation) in a subject with preserved peak expiratory flow (PEF) and forced vital capacity (FVC). Here AEX_3 >>AEX. (D) Graphic example of AEX_3 in a patient with restriction to ventilation in whom AEX_3 <AEX. (E) AEX_3 in a patient with a mild mixed pattern (obstruction and restriction), in which both overestimation and underestimation are possible. Dotted lines illustrate isovolumic predicted normal expiratory flows. Red: obstruction; blue: restriction; green: mixed ventilatory pattern. AEX, area under the expiratory flow–volume curve.

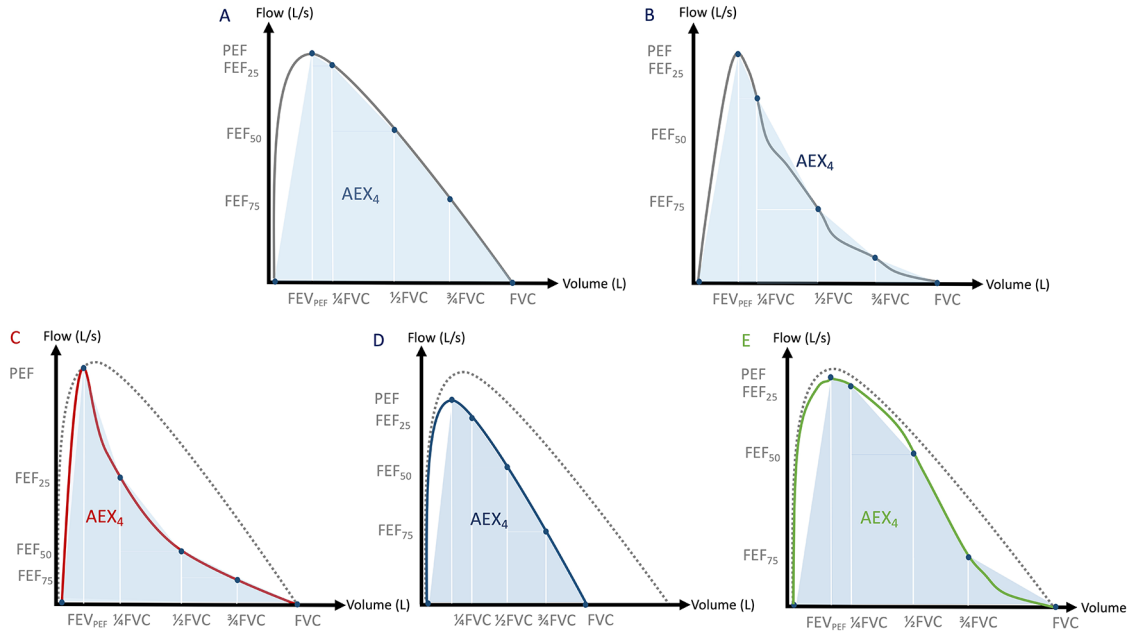

Figure 6 (A) Graphic example of AEX_4 in a normal subject in whom AEX_4 <AEX. (B) Representation of AEX_4 in a subject with normal spirometry (all flows and volumes are above lower limits of normal) and 'concave' appearance of the flow–volume curve. Here AEX_4 >AEX (overestimation due to the concavity of the curve). (C) AEX_4 in obstruction (airflow limitation) in a subject with preserved peak expiratory flow (PEF) and forced vital capacity (FVC). Here AEX_4 >>AEX. (D) Graphic example of AEX_4 in a patient with restriction to ventilation in whom AEX_4 <AEX. (E) AEX_4 in a patient with a mild mixed pattern (obstruction and restriction), in which both overestimation and underestimation are possible. Dotted lines illustrate isovolumic predicted normal expiratory flows. Red: obstruction; blue: restriction; green: mixed ventilatory pattern. AEX, area under the expiratory flow–volume curve.

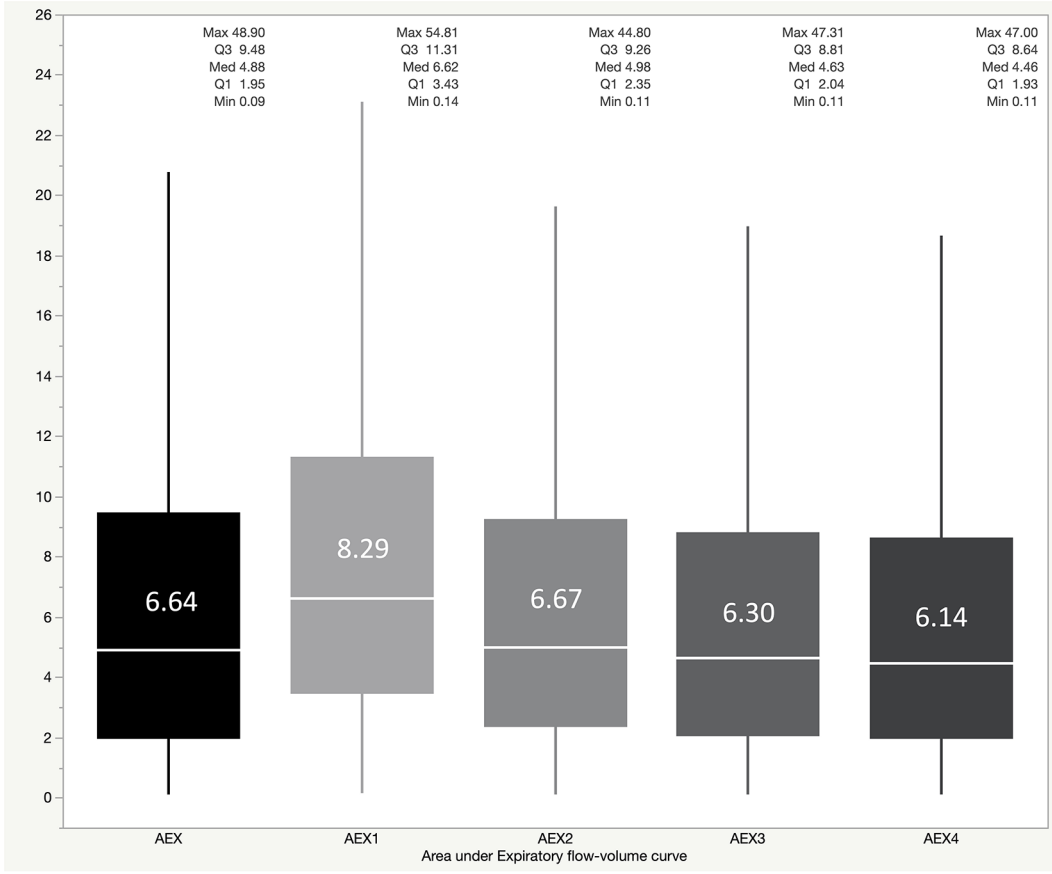

Figure 7 Box-and-whisker plot representing AEX (black), AEX_1, AEX_2, AEX_3 and AEX_4 (lighter to darker gray). The white lines inside the boxes represent medians; the ends of the boxes are represented by the 25th (Q1) and the 75th (Q3) quartiles. The lengths of the whiskers are determined by the points falling within 1.5 * IQR (Q3–Q1) below Q1 and above Q3, respectively. Means (white font) are shown inside the box plots. Outliers are not represented on the graph. AEX, area under the expiratory flow–volume curve.

When the four AEX approximations (AEX_1 to AEX_4) were analyzed in subjects with and without various lung diseases, they were significantly lower in patients with diagnoses of chronic obstructive pulmonary disease (COPD) or emphysema, perhaps as the result of the physiologic interplay between loss of parenchymal elastic recoil (predominant in emphysema) and higher airway resistance in the small conduits. In subjects with chronic bronchitis and in intercritical asthma (ie, in-between exacerbations), no significant differences were noted.

Our previous work showed that AEX compared favorably with traditional spirometric parameters in diagnosing physiologic respiratory derangement and in estimating the severity of impairments. Furthermore, the actual AEX was able to predict with good accuracy inspiratory capacity, inspiratory capacity/total lung capacity and residual volume/total lung capacity ratios and thus reducing the need for lung volume testing.[5 17] The current investigation extends the value of the area under expiratory flow–volume loop concept by showing that it can be closely and easily approximated using universally available spirometric variables. This applies especially when existing software does not compute and report the actual AEX values. A preliminary survey of four major PFT equipment manufacturers in our market identified that, in practice, AEX is currently available in only one platform.

The current work also extends prior evaluations of AEX, which have primarily been used in pediatric testing for assessing bronchoconstriction or bronchodilation responses.[18 19 21 22] In a recent article, the authors effectively constructed predicted AEX_4 (called 'reference flow-volume loop') and compared it against actual AEX, thus assessing the degree of airway hyperinflation in adult patients with COPD.[23] The authors confirmed our prior findings that AEX performs well in diagnosing and stratifying the severity of functional impairments,[5 17] showing that AEX*100/predicted AEX_4 has an excellent discriminating capacity for severe hyperinflation in COPD. To our knowledge, the current study is the first to compare potential approximations of AEX ($AEX_{1–4}$) with actual AEX and their use as alternative parameters in interpreting PFT by spirometry.

The strengths of our investigation are the large data set of PFTs (n=15 308) performed on a very diverse patient population and pathologies, methods used that included decision tree partitioning using both a training (66%) and a validation (33%) group, and high-power forest bootstrap models for assessing the performance of the investigated parameters. Potential weaknesses of our study are the availability of data from a single center, the lack of specific detail regarding underlying diagnoses, and the absence of patient follow-up or long-term outcomes. To overcome this latter weakness, we are currently examining the diagnostic performance of

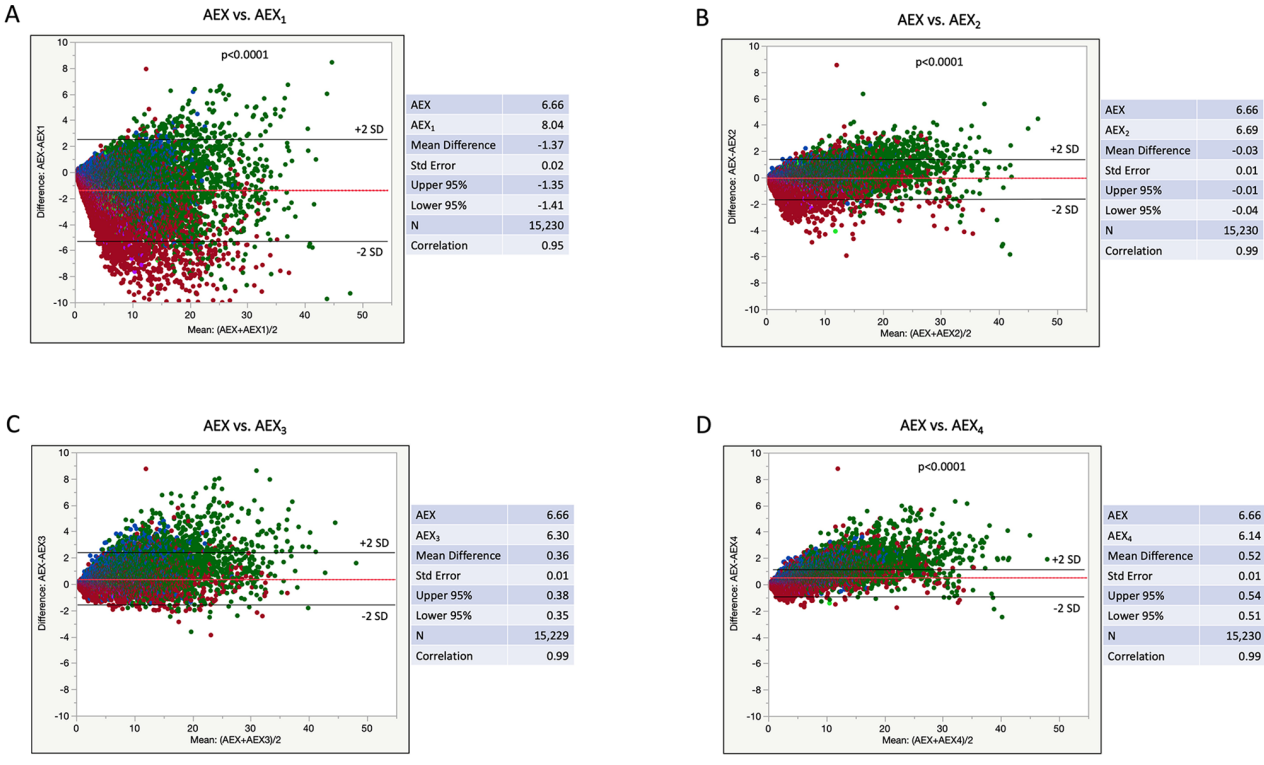

Figure 8 Bland-Altman diagrams showing the differences between AEX and the approximated parameters (AEX_1, AEX_2, AEX_3 or AEX_4) on the Y axes versus their averages on the X axes. (A) AEX_1: wide dispersion, overall overestimation (B) AEX_2: smaller dispersion and very small average overestimation (C) AEX_3: smaller dispersion and average underestimation (D) AEX_4: the smallest dispersion. Marker color codes: green: normal, red: obstruction; blue: restriction; purple: mixed ventilatory defect (all based on Global Lung Initiative predictive equations and splines). Red lines: mean differences; black lines: two SDs (plus or minus, SD) of the differences. AEX, area under the expiratory flow–volume curve.

these parameters in other PFT data sets from other patient populations in a different center, that is, Atlanta Veterans' Affairs PFT Laboratory. We expect that this examination of generalizability and clinical validation of these findings will be the subject of a separate, future publication.

CONCLUSION

This study analyzes the performance of several approximations of the AEX based on instantaneous flows at peak expiration and at predetermined volumes (eg, FEF_{25}, FEF_{50} and FEF_{75}). The parameter AEX_4 performs with acceptable accuracy as a surrogate marker or approximation of AEX, which makes it potentially useful in diagnosing physiologic derangement of pulmonary function and in stratifying the severity of such impairment. Further validation of these new spirometric measurements in discrete data sets is needed and is currently being assessed.

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