Development and Evaluation of a Small Airway Disease Index Derived From Modeling the Late-Expiratory Flattening of the Flow-Volume Loop

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Excessive decrease in the flow of the late expiratory portion of a flow volume loop (FVL) or “flattening”, reflects small airway dysfunction. The assessment of the flattening is currently determined by visual inspection by the pulmonary function test (PFT) interpreters and is highly variable. In this study, we developed an objective measure to quantify the flattening. We downloaded 172 PFT reports in PDF format from the electronic medical records and digitized and extracted the expiratory portion of the FVL. We located point A (the point of the peak expiratory flow), point B (the point corresponding to 75% of the expiratory vital capacity), and point C (the end of the expiratory portion of the FVL intersecting with the x-axis). We did a linear fitting to the A-B segment and the B-C segment. We calculated: 1) the AB-BC angle (\(\angle ABC\)), 2) BC-x-axis angle (\(\angle BCX\)), and 3) the log ratio of the BC slope over the vertical distance between point A and x-axis [log (BC/A-x)]. We asked an expert pulmonologist to assess the FVLs and separated the 172 PFTs into the flattening and the non-flattening groups. We defined the cutoff value as the mean minus one standard deviation using data from the non-flattening group. \(\angle ABC\) had the best concordance rate of 80.2% with a cutoff value of 149.7\(^\circ\). We then asked eight pulmonologists to evaluate the flattening with and without \(\angle ABC\) in another 168 PFTs. The Fleiss’ kappa was 0.320 (lower and upper confidence intervals [CIs]: 0.293 and 0.348 respectively) without \(\angle ABC\) and increased to 0.522 (lower and upper CIs: 0.494 and 0.550) with \(\angle ABC\). There were 147 CT scans performed within 6 months of the 172 PFTs. Twenty-six of 55 PFTs (47.3%) with \(\angle ABC < 149.7\)\(^\circ\) had CT scans showing small airway disease patterns while 44 of 92 PFTs (47.8%) with \(\angle ABC \geq 149.7\)\(^\circ\) had no CT evidence of small airway disease. We concluded that \(\angle ABC\) improved the inter-rater agreement on the presence of the late expiratory flattening in FVL. It could be a useful addition to the assessment of small airway disease in the PFT interpretation algorithm and reporting.

Keywords: small airway disease, pulmonary function test, spirometry, machine learning, CT scan
INTRODUCTION

Small airways traditionally refer to the peripheral airways with an internal diameter of <2 mm (Ranga and Kleinerman, 1978). They are often considered the “quiet” zone since a disease process occurring in this region is difficult to detect clinically (Mead, 1970). This is in part because small airways that are arranged in parallel normally contribute only a small fraction of the airway resistance due to their large total cross-sectional area (Macklem and Mead, 1967). Small airway obstruction does not decrease the FEV1/FVC ratio, which is a measure of proximal airway function. Therefore, identifying small airway disease in pulmonary function test (PFT) represents a challenging task for the interpreters who use the current rules-based interpretation algorithm.

Changes in some parameters in PFT have been considered to infer small airway dysfunction (McNulty and Usmani, 2014). For example, increased RV/TLC indicates air trapping due to airway obstruction but is not specific to small airways (Sorkness et al., 2008). A decrease in the forced expiratory flow at 25–75% of FVC (FEF25–75%) is commonly cited to reflect small airway dysfunction, but it is highly variable and the value is dependent on the FVC and expiratory effort (McFadden and Linden, 1972; Boggs et al., 1982; Tager et al., 1998). The ratio of the airflow rate of 50% vital capacity to the airflow rate of 25% vital capacity (V50/V25) correlated with the difference between the R5 and R20 (R5–R20) values measured by impulse oscillometry (Suzuki et al., 2015). The forced expiratory flow at 50% FVC (FEF50%) was reduced in asymptomatic smokers who likely had small airway disease (Dosman et al., 1975). A FEF50% value less than 70% identified about 45% of patients with cough-variant asthma who had normal proximal airway function, a small airway disease phenotype (Yuan et al., 2019). Like FEF25–75%, these two measurements are also dependent on expiratory effort. Excessive decrease in the flow toward the end of the expiratory portion of a flow volume loop (FVL) or “flattening” reflects premature closure of small airways and is less effort dependent (Mead et al., 1967; Permutt and Menkes, 1979; Macdonald and Cole, 1980; Menkes et al., 1981). Studies have shown that the flow in this portion of the curve is less affected by breathing a helium-oxygen mixture, supporting the contention that this portion is from the small airways where the flow tends to be laminar and thus less density-dependent (Fox et al., 1974; Macdonald and Cole, 1980; Konstantinos Katsoulis et al., 2016).

The “flattening” is currently assessed by visual inspection of FVL by the PFT interpreters. It is subject to significant inter-rater variabilities (Hnatiuk et al., 1996). The current study sought to develop an objective index to quantify the extent of the late-expiratory flattening of the FVL. We digitized the FVLs directly from the PFT reports in PDF format from the electronic medical records and reconstructed the FVLs for the mathematical modeling. We tested the hypothesis that the availability of an objective measure to the raters would help decrease the inter-rater variability in the late-expiratory flattening of FVL. We also compared the agreement between the measure and the CT scan of the chest.

METHODS

All PFTs in this study were performed between 1/1/2018 and 10/31/2019. We downloaded the PFT reports from the Duke electronic medical record system (EPIC) that were in PDF format. PFTs that had FEV1/FVC >0.7 were selected. We digitized and extracted data points of the FVLs using a custom tool written in Python (version 3.7) (https://peps.python.org/pep-0537/). The study was approved by the Duke Institutional Review Board (Pro00105365).

Flow Volume Loop Extraction and Digitization

To quantify the late expiratory flattening of the FVL, we first extracted and digitized the expiratory portion of the FVL. Since all PFT reports had the same layout with the FVL in the right upper corner as shown in Figure 1A, we identified and located the FVL by searching for the label highlighted by the red box (F/V ex) in Figures 1A,B. We calculated the image hash of the label and then conducted a search for the same hash value in the PDF report. The search was able to identify and locate the FVL in all reports. After we obtained the FVL, the x and y axes were aligned to place the pixel points along the expiratory portion of the FVL to the correct x and y scales. We first calculated the image hash of number samples such as the numeric number “2” in Figure 1B. After searching for the same image hash in the FVL, we were able to locate the number “2” on both x-axis and y-axis. Offsets were applied to the number positions so that we identified the exact tick positions for the number “2” on x and y-axis. Based on the positions of the values on the axis, we obtained the mapping coefficients describing the relationship between the pixel values and the actual value on both x and y directions. After the alignment, we picked up the data points on the curve by differentiating the pixel color from the background. These procedures allowed digitization of the expiratory portion of the FVL, which could be executed automatically.

Quantification of Expiratory Portion of the Flow Volume Loop

After digitizing the expiratory portion of the FVL, we located the points A, B, and C on the curve as shown in Figure 2. Point A is the highest point of curve (peak expiratory flow). Point B is the point on the curve correponding to 75% of the expiratory vital capacity, which roughly corresponds to the start of small airways (Mead et al., 1967; Wood and Bryan, 1969; Gelb and Klein, 1977). Point C is the end of the curve where the expiratory portion of the FVL intersects the x-axis. The A-B line segment (orange line) and the B-C line segment (green line) were used for analysis (Figure 2). We used three methods to quantify the flattening of the late expiratory portion of the FVL. These methods were designed to simulate how the clinicians visually assess the late
flattening of the FVL. 1) AB-BC angle (∠ABC) is the angle between the linear fitting of AB and BC. 2) BC-x-axis angle (∠BCX) is the angle between the linear fitting of BC and the x-axis. 3) Normalized BC slope is the ratio of the BC slope over peak flow or the vertical distance (dash line) between A and x-axis (A-x). The orange line is the linear fitting of the AB segment. The red line with dash line extension is the linear fitting of the BC segment.

![FIGURE 1](image1.png) A typical PFT report in the electronic medical record system used by Duke University Medical Center (EPIC). The label highlighted by the red box is used as an identifier to locate the flow volume loop (FVL) on the page. (B) The target FVL extracted by the algorithm; (C) The green dots and the orange dots are used for y-axis and x-axis alignment respectively. The red dot indicates the point of the peak expiratory flow.

Statistical Analysis
All data are expressed as mean ± standard deviation (SD). Comparison between the two groups were performed using the unpaired student’s t-test. The concordance rate was calculated as the total number of the tests that are concordant over the total number of tests assessed. The inter-rater agreement with and without the quantification of the flattening was assessed by the Fleiss’ kappa test Fleiss and Cohen (1973). All statistical analyses were performed using Python SciPy 1.0 (Virtanen et al., 2020). A \( p < 0.05 \) was considered statistically significant.

RESULTS
Determination of the Presence of the Late Expiratory Flattening of the Flow Volume Loop
We selected 172 PFTs that had FEV1/FVC > 0.7 with adequate FVL quality. We calculated ∠ABC, ∠BCX, and BC/A-x. The distributions of ∠ABC and ∠BCX were close to Gaussian (Figures 3A, B) while the distribution of BC/A-x was skewed to the right (Figure 3C). After a log transformation, the distribution of BC/A-x approximated Gaussian (Figure 3D) and the index termed log (BC/A-x) was used for subsequent analysis.

Absent any additional information, an expert pulmonologist evaluated the FVLs of all 172 PFT reports to separate the tests with late expiratory flattening (\( n = 64 \)) from those without (\( n = 108 \)). The three metrics were computed for the flattening and the non-flattening groups. As shown in Figure 4, the mean values of ∠ABC for the flattening group and the non-flattening group were 144.8 ± 8.5° and 163.8 ± 14.1°, respectively (\( p < 0.0001 \)). The mean
FIGURE 3 | Histogram distributions of $\angle ABC$, $\angle BCX$, BC/A-x, and log (BC/A-x). The distributions of $\angle ABC$ (A) and $\angle BCX$ (B) are close to Gaussian while the distribution of BC/A-x (C) is skewed to the right. After log transformation, the distribution of log (BC/A-x) approximated Gaussian (D).

FIGURE 4 | Differences in $\angle ABC$, $\angle BCX$, and log (BC/A-x) between the flattening and the non-flattening groups. The flattening and the non-flattening groups were identified by an expert pulmonologist. *: $p < 0.0001$. 
The ability to identify small airway disease by PFT can help clinicians make early clinical decisions and potentially give a more accurate prognosis. For example, an increase in the ratio of the airflow rate of 50% vital capacity to the airflow rate of 25% vital capacity, a small airway disease marker, in the pretransplant pulmonary function test (PFT) was associated with poor survival following allogeneic hematopoietic cell transplantation (Nakamae et al., 2016). A forced expiratory flow at 50% FVC (FEF50%) less than 70% identified about 45% of patients with cough variant asthma who had normal proximal airway function, suggesting probable small airway disease phenotype (Yuan et al., 2019). Our small airway
disease index ($\triangle ABC$) was able to identify about 50% of the patients who had CT evidence of small airway disease. Since PFTs are usually performed prior to the CT scan in outpatient visits, this can increase the pretest probability for the small airway disease and further justifies and facilitates the ordering of the CT scan.

The process described in our study for digitization, extraction and mathematic modeling can be customized for PFT reports that have different layout than ours. Specifically, the position of FVL on the report and the X-Y axes can be located by different user-defined parameters. With proper coding, the process can be automated to generate $\triangle ABC$. The precision of the modeling requires that the PFT reports contain reasonably good quality FVLs. Therefore, clinician discretion remains an essential element in the interpretation.

In this study, we used (mean $-$ 1 SD) to define the lower cutoff value (or approximately 15th percentile). In the latest PFT interpretation guidelines, the use of the lower limit of normal (LLN) or the 5th percentile, was recommended (Culver et al., 2017). The LLN for $\triangle ABC$ was 140.8°. If the LLN was used, 17 PFTs had $\triangle ABC$ less than LLN and 6 of them (35.3%) had CT evidence of small airway disease. LLN, however, is affected by age and patient’s physical measurements. Aging is known to be associated with loss of small airway function even in subjects without airway obstruction (Martinez et al., 2017). A reference equation for $\triangle ABC$ can be generated using a larger number of PFTs and should be done in future studies.

In summary, we have developed an algorithm to digitize and extract FVL from the PFT reports in PDF format and calculated an index ($\triangle ABC$) using a mathematic modeling approach that can quantify the late expiratory flattening of the FVL. This index derived from the graphic analysis of the FVL could assist the interpreters in determining whether the late flattening was present with more confidence and thus decrease the inter-rater variability. It could be a useful addition to the assessment of small airway disease in the PFT interpretation algorithm and reporting.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Ethical reasons since the database include patients’ personal health information. Requests to access these datasets should be directed to Yuh-Chin Huang, yuhchin.huang@duke.edu.

AUTHOR CONTRIBUTIONS

HC, CH, Y-CH, and PG: concept, study design. HC, CH, and Y-CH: data analysis, manuscript preparation. Y-CH, SJ, AO, A-KW, DS, ST, LT, JA, and PG: data validation, manuscript preparation.

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