Assessment of bronchial obstruction and its reversibility by shape indexes of the flow-volume loop in asthmatic children

Amaury Berrier[1], Angelica Tiotiu[1], Claude Bonabel[2], Phi linh Nguyen Thi[2], David Richard[2], Silvia Demoulin-Alexikova[2], Cyril Schweitzer[3], and Iulia Ioan[2]

[1]CHRU de Nancy
[2]CHRU Nancy
[3]Centre Hospitalier Régional Universitaire de Nancy

August 28, 2020

Abstract

Asthma assessment by spirometry is challenging in children as forced expiratory volume in one second (FEV1) is frequently normal at baseline. Bronchodilator (BD) reversibility testing may reinforce asthma diagnosis but FEV1 sensitivity in children is controversial. Ventilation inhomogeneity, an early sign of airway obstruction, is described by the upward concavity of the descending limb of the forced expiratory flow-volume loop (FVL)s, not detected by FEV1. The aim was to test the diagnosis ability of FVL shape indexes as β-angle and forced expiratory flow at 50% of the forced vital capacity (FEF50)/peak expiratory flow (PEF) ratio, to identify asthmatics from healthy children in comparison to "usual" spirometric parameters. Seventy-two asthmatic children and twenty-nine controls aged 8 to 11 years were prospectively included. Children performed forced spirometry at baseline and after BD inhalation. Parameters were expressed at baseline as z-scores and BD reversibility as percentage of change reported to baseline value (Δ%). Receiver operating characteristic curves were generated and sensitivity and specificity at respective thresholds reported. Asthmatics presented significantly smaller zβ-angle, zFEF50/PEF and zFEV1 (p[?]0.04) and higher BD reversibility, significant for Δ%FEF50/PEF (p=0.02) with no difference for Δ%FEV1. zβ-angle and zFEF50/PEF exhibited better sensitivity (0.58, respectively 0.60) than zFEV1 (0.50), and similar specificity (0.72). Δ%β-angle showed higher sensitivity compared to Δ%FEV1 (0.72 vs 0.42), but low specificity (0.52 vs 0.86). Quantitative and qualitative assessment of FVL by adding shape indexes to spirometry interpretation may improve the ability to detect an airway obstruction, FEV1 reflecting more proximal while shape indexes peripheral bronchial obstruction.

Introduction

Early diagnosis and treatment of asthma, the most frequent chronic disorder in children, are important to prevent consequences as bronchial remodeling, infantile morbi-mortality and economic burden[1]. Asthma phenotypes, guidelines and therapies have evolved over past years [2], justifying continuous patient care optimization. Accordingly, lung function testing has a pivotal role in the initial assessment, follow-up and monitoring the response to treatment, being an essential contributor to management. Pediatric spirometry has undergone substantial improvement in standardization and measurement [3-5]. The forced expiratory flow-volume loop (FVL) is readily obtained by miniaturized, easy-to-handle electronic flowmeters with numerical transformation of physiological signals. This test is accessible, not expensive and simple to use in routine clinical practice. The gold standard outcome, the forced expiratory volume in 1 s (FEV1), is the most reproducible spirometric parameter, reflecting bronchial caliber and being correlated to asthma severity and mortality risk [6,7]. Bronchodilator (BD) reversibility of FEV1 is also fundamental for initial diagnosis and severity assessment, being a predictor of poor control in mild to moderate asthma [8] and of response to inhaled corticosteroids [9]. However, FEV1 sensitivity to detect an airway obstruction and /or its BD reversibility has been disputed in children. This is probably because FEV1 mostly reflects proximal bronchial

obstruction while incipient asthmatic impairment is primarily located in peripheral airways[10]. An early sign of peripheral involvement seems to be the occurrence of ventilation inhomogeneity between different lung regions, owing to unevenly airway smooth muscle contraction, mucosal edema and small airway closure [11]. This inhomogeneity was shown to be present even in asthmatic children considered to be clinically controlled and with respiratory function within normal limits[12]. During a forced expiration maneuver, the choke point, where dynamic compression starts, might not be homogeneously distributed in asthmatic lungs, depending on the parallel peripheral resistances. Therefore, whereas healthy lungs will empty uniformly across the forced expired volume, asthmatic lungs will show a successive inhomogeneous emptying of territories, as expected from a model with different time constants [13], resulting in an upward concavity of FVL. Some indexes were previously described to characterize the shape of FVL [13-15]. β-angle, the aperture between 2 lines passing through forced expiratory flow at 50% of the forced vital capacity (FEF50), one crossing the point at the end of forced expiration corresponding to residual volume, and the other a point situated at the height of peak expiratory flow (PEF) on y axis, indicates an upward convexity or concavity respectively when it is greater or smaller than 180° [16]. β-angle has been shown to be a robust variable with good reproducibility and feasibility in adults [16], preschool [17] and school children [18,19]. A simplified approach to estimate β-angle is to compute FEF50/PEF ratio that presents diagnostic performances equivalent to β-angle [17].

To overcome the difficulty of interpreting a FVL in children based on a single parameter, *i.e.* FEV1 that lacks sensitivity, we hypothesized that shape indexes, *i.e.* β-angle and FEF50/PEF, might be considered in routinely clinical practice to ameliorate diagnosis capacity of spirometry in identifying the presence of an airway obstruction and its BD reversibility. The aim of this study was to determine which parameter at baseline and after BD administration expressed as percentage of change from baseline (Δ%), has the best performance in identifying asthmatics from healthy children. The secondary aim was to assess the diagnosis ability of an association of shape indexes with "usual" spirometric parameters.

Material and methods

Subjects.

Asthmatic and healthy children were prospectively included in this study. Asthma was diagnosed by a pediatric pulmonologist based on Global Initiative for Asthma guidelines and children were referred to the lab for a routine follow-up lung function testing. Long acting BD agents were withdrawn for >12 hours and short acting BD agents for >6 hours before the day of study. The presence of asthma symptoms in the last 3 months and chronic anti-asthmatic therapy as inhaled steroids associated or not with long acting BD agents and leukotriene antagonists were documented. Measurements included subject's weight, height, transcutaneous oxygen saturation and clinical examination consisted in cardiopulmonary auscultation. Age-matched healthy children were recruited from local primary schools. All children were free of respiratory infection for at least one month before the day of testing. Written informed consent was obtained from the children and their parents at the time of lung function testing. The study was approved by the Ethics Committee (Comité de Protection des Personnes Est III, Centre Hospitalier Universitaire de Nancy, France).

Lung function testing .

Forced spirometry was performed by an experienced technician using electronic flowmeters with computer animation software (Masterscope Erich Jaeger GmbH, Wuertzburg, Germany) according to current recommendations [3,20]. The maneuver was explained to the child who was then trained to perform a full inspiration followed by a forced expiration with typical fast rise to PEF and uniform decrease throughout expiration. Usually five maneuvers were necessary until two reproducible FVL's were achieved. The curve with the best sum between forced vital capacity (FVC) and FEV1 was retained for analysis. Two puffs of salbutamol (Ventoline 100 µg/puff, Glaxo-SmithKline, Marly Le Roi, France) were then administered to the child using an inhalation chamber (Nespacer, Astra France, Monts, France) and forced spirometry repeated after 10 minutes. FVC, FEV1, FEV1/FVC and forced expiratory flow between 25% and 75% of the FVC (FEF25-75%) expressed in absolute values and z-scores [21], at baseline and their response to BD, expressed as z-score and percentage of change reported to baseline (Δ%), were retained for analysis. Part of the spirometric data

has already been published [22]. For this study, shape indexes, β-angle (*figure 1*) and FEF50/PEF ratio, were computed, as absolute values (β-angle formula being: $\beta = 180 - \tan^{-1}[(PEF - FEF50) / (0.5 \times FVC)] + \tan^{-1}[FEF50 / (0.5 \times FVC)]$[16]and z-scores as previously reported [5] and retained for analysis.

Statistical analysis .

The analysis was performed using SAS University Edition statistical software. The qualitative variables were expressed as number (percentage) and the quantitative variables as median [25^{th}; 75^{th} percentiles] as not normally distributed. Mann-Whitney test was used to compare patients and controls. The diagnostic performance was tested for each parameter using Receiver Operating characteristic Curves (ROC) and area under ROC curve (AUC) and its 95% confidence interval (95CI), sensitivity and specificity at the most relevant thresholds, reported. AUC (95CI), sensitivity and specificity were also computed for the combination of spirometric parameters at the respective thresholds. A p value$<$*0.05* was considered statistically significant.

Results

Seventy-two asthmatics (44 boys) and 29 healthy children (13 boys), aged 8 to 11 years, were included in this study. 49(68%) asthmatic children had no symptoms during the last 3 months while 23 patients (32%) had symptoms as chronic dry cough in 14(61%) or cough/wheezing on exertion in 9(39%). Thirty-two patients (44%) had no anti-asthmatic treatment while 40(56%) were treated by inhaled steroids alone in 10 (14%), or associated with leukotriene antagonist in 2 (3%), with long-acting BD agent in 9 (13%), or both in 9 (13%). 10 (14%) asthmatics had leukotriene antagonist alone.

Patients' characteristics and spirometric parameters at baseline, expressed as absolute value or z-score, and their BD responses expressed as Δ%, are presented in *table 1* . The two populations were similar for age, height, weight and body mass index. FVC and zFVC were not different between the two groups. Asthmatics had significantly smaller absolute values and z-scores for FEV1 (*p=0.003* , respectively *p=0.04*), FEV1/FVC (*p=0.002 for both*), FEF25-75% (*p=0.0003,* respectively, *p=0.004*), FEF50/PEF (*p=0.01* , respectively *p=0.007*) and β-angle (*p=0.009* , respectively *p=0.006*) than healthy children. More asthmatics, 32 (44%), than controls, 7 (24%), had β-angle $<180°$ or FEF50/PEF <0.05 that define a concave shape of FVL but without statistical significance. 10 (14%) asthmatic children had zFEV1/FVC <-1.64 associated with zFEV <-1.64 in 6 (8%) of them.

Spirometric parameters after BD inhalation, expressed in z-score, were lower in asthmatics than controls but without statistical significance, except for zFEV1/FVC-bd (*p=0.02*) (supplementary table).

BD responses showed no difference for Δ%FEV1 between asthmatic and control children. Asthmatics presented higher BD responses compared to controls statistically significant for Δ%FEV1/FVC (*p=0.04*) and Δ%FEF50/PEF (*p=0.02*), but not for Δ%β-angle (p=0.07).

The comparison between the 23 (32%) asthmatic children presenting respiratory symptoms during the last 3 months and the 49 (68%) asymptomatic patients is presented in *table 2* . Age, weight and height were comparable in both groups. zFEV1 was similar and zFEV1/FVC, zFEF25-75%, zFEF50/PEF and zβ-angle were lower in the group of children with symptoms *vs* no-symptoms but without statistical significance. BD change was not different between the 2 groups for Δ%FEV1 and Δ%FEV1/FVC but it was significantly higher in asthmatics with symptoms for Δ%FEF50/PEF and Δ%β-angle, reported to the asymptomatic group (*p=0.02*).

ROC curves are represented for the different parameters at baseline in z-score in *figure 2* and for their BD reversibility in*figure 3* . AUC (95CI), sensitivity, specificity and respective cut-offs are presented in *table 3* for the parameters at baseline in z-score, for their BD reversibility expressed as Δ%, and their combination.

At baseline, zFEV1/FVC, zβ-angle or zFEF50/PEF presented similar AUC's, slightly more elevated than zFEV1's AUC (*figure 2*). The spirometric parameters exhibited different patterns of sensitivity and specificity, *i.e.* zFEF50/PEF and zβ-angle showed the best sensitivity while specificity was similar for zFEV1, zβ-angle or z-FEF50/PEF (*table 3*). When combining the spirometric parameters, the AUC's improved and

best sensitivity was obtained when considering zFEV1+zβ-angle or zFEV1+z-FEF50/PEF, at the respective thresholds, while best specificity was obtained for zFEV1/FVC+zFEF50/PEF (*table 3*).

ROC curves for BD reversibility showed larger AUC for Δ%FEF50/PEF, followed by Δ%FEV1/FVC and Δ%β-angle (*figure 3* and *table 3*). Sensitivity was best for Δ%β-angle or Δ%FEF50/PEF and very low for Δ%FEV1 (*table 3*). Specificity was best for Δ%FEV1 and low for Δ%β-angle. The association of parameters improved the AUC's but not the sensitivity – specificity.

Discussion

Our study conducted in schooler asthmatic children found significantly lower lung function at baseline in patients compared to healthy controls, either "usual" spirometric parameters or shape indexes, and higher BD reversibility. Shape indexes were found to be slightly more sensitive in identifying asthmatic children at baseline than zFEV1 with the same specificity while their BD reversibility showed high sensitivity and low specificity compared to Δ%FEV1. Conversely, specificity was higher for Δ%FEV1.

Qualitative and quantitative assessment of the descending limb of the FVL and its variability with airway obstruction have already been addressed in past studies, by visual examination or objective measures[13,14,23,24]. β-angle, constructed to transcribe the curvature of the FVL into a single numerical value [16], is the angle between the first and second half of the FVL at the point of maximum flow point at mid pulmonary volume. β-angle and its simplified estimate, FEF50/PEF, in absolute values or z-scores, were significantly lower at baseline in our school-aged asthmatic children compared to healthy subjects, in keeping with previous reports demonstrating more concave FVL configuration measured by smaller β-angle in asthmatic preschoolers [17] or schoolers[18,19,25].

When testing the diagnostic value to separate asthmatics from controls in our population, AUC's were similar for zβ-angle or zFEF50/PEF and "usual" spirometric parameters, with relatively lower AUC for zFEV1 (*figure 2* and *table 3*). zβ-angle and zFEF50/PEF showed slightly higher sensitivity than zFEV1 suggesting that the presence of an early airway obstruction is rather detected by indexes describing FVL curvature than by zFEV1. The specificity was the same for zβ-angle and zFEF50/PEF or zFEV1 (*table 3*). A recent report in schooler asthmatics found large AUC and sensitivity for β-angle and, in contrast to our study, FEV1 sensitivity was also high while β-angle and FEV1's specificities were very low [18]. The different patterns of sensitivity – specificity at baseline indicate that a significant proportion of false diagnosis of asthma would result if solely shape indexes would be taken in consideration to identify airway obstruction.

FEV1, the gold standard parameter for diagnosing an airway obstruction, is obtained in the first second of the forced expiration, situated on the effort-dependent part of FVL. Thus, FEV1 would theoretically be more affected by subject's effort than distal flows (*i.e.* FEF50 reported here) located on the second part of forced expiration, considered effort-independent once airway dynamic compression has occurred. Nevertheless, FVL shape is highly conditioned by child's cooperation and comprehension to perform an optimal, sustained expiratory effort, to obtain a reproducible PEF and a complete expiration to attain the residual volume. This maneuver is easily acquired with appropriate guidance and encouragement from experienced technicians in a pediatric lung function testing lab, but caution must be taken when interpreting a pediatric FVL.

To improve the diagnostic ability of spirometric parameters to detect asthma in children, we investigated whether the combination of shape indexes with "usual" spirometric parameters will improve their discriminating power. AUC's improved and the best sensitivity was obtained when shape indexes were associated with zFEV1 and the best specificity when they were associated with zFEV1/FVC (*table 3*), in agreement with recent reports demonstrating that the association of quantitative and qualitative parameters may enhance the diagnosis accuracy [18,25].

Our study confirms and extends these observations by testing the BD reversibility of shape indexes and "usual" spirometric parameters and shows larger BD responses for shape indexes in asthmatics than controls, with no difference for Δ%FEV1 (*table 1*). Furthermore, Δ%β-angle and Δ%FEF50/PEF were significantly higher in symptomatic than in asymptomatic asthmatic children (*table 2*), but not BD response of the

other spirometric parameters. Δ%β-angle exhibited high sensitivity and low specificity contrary to Δ%FEV1 showing low sensitivity and high specificity (*table 3*). A significant decrease in the upward concavity of the FVL after short-acting BD inhalation have previously shown for other shape indexes in asthmatic children aged 5 to 12y[15] and adults [24] or after 8 weeks of inhaled corticosteroids in young adults [14].

The effect of short acting BD in asthma is dependent on complex interactions between airway caliber, ventilation and lung perfusion distribution, ventilation-to-perfusion ratio, and cardiac output[26]. Short acting BD may have contradictory effects related to its action on distribution of ventilation – perfusion inequalities that may improve, worsen or not change[27]. BD might act on peripheral airway obstruction with improvement of gas mixing and, consequently, of FVL shape. Contrarily, BD may also worsen gas mixing as partially opens up previously full closed airways, that will become inhomogenously ventilated regions with slow emptying during expiration [26], resulting in no change in FVL curvature.

The aim of our study was to investigate the BD reversibility of shape indexes in the context of a lung function testing lab, procedure routinely used in the diagnosis and follow-up of asthmatic children. Our studied children had less severe asthma with normal baseline lung function in the majority (zFEV1/FVC <-1.64 in less than a fifth) and anti-asthmatic treatment in more than half that might partly underestimate the BD change. Nevertheless, our data suggest a positive effect of BD inhalation on FVL shape, especially in symptomatic asthmatics, with high sensitivity for Δ%β-angle and high specificity for Δ%FEV1 to separate asthmatics from healthy children. Accordingly, considering exclusively Δ%FEV1 as optimal diagnostic tool for reversibility assessment as stated in a number of international guidelines [3,28,29], would result in a large number of false negatives.

In conclusion, our study confirms previous reports that the shape of FVL should be taken in consideration when interpreting a forced spirometry in children. Shape indexes and FEV1 at baseline and their BD reversibility had about the same diagnostic value in detecting airway obstruction but with a different pattern of sensitivity – specificity, being complementary. Quantitative and qualitative assessment of FVL may improve the ability to detect airway obstruction, FEV1 reflecting more proximal while shape indexes peripheral, distal bronchial obstruction. Future perspectives will imply to assess more frequently in practice the association of different lung function parameters by establishing a spirometry score based on shape indexes and "usual" spirometric values, easy to compute and to integrate into spirometers' software, in order to improve asthma diagnostic or to assess the long-term benefit of anti-asthmatic therapies in pediatric population.

Acknowledgements

The authors thank the children that contributed to the study and their families, and gratefully acknowledge Professor François Marchal for careful editorial work and the technical assistance of Sylvie Meline, Francine Cael, Marianne Mougin, Myriam Chamagne and Marie Jeanne Arnoux.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2019. Available from:*www.ginasthma.org.* . 2019.

2. Gauthier M, Ray A, Wenzel SE. Evolving Concepts of Asthma. *Am J Respir Crit Care Med.* 2015;192(6):660-668.

3. Beydon N, Davis SD, Lombardi E, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med.*2007;175(12):1304-1345.

4. Boutin B, Koskas M, Guillo H, et al. Forced expiratory flows' contribution to lung function interpretation in schoolchildren.*Eur Respir J.* 2015;45(1):107-115.

5. Neve V, Edme JL, Baquet G, Matran R. Reference ranges for shape indices of the flow-volume loop of healthy children. *Pediatr Pulmonol.* 2015;50(10):1017-1024.

6. Duong M, Islam S, Rangarajan S, et al. Mortality and cardiovascular and respiratory morbidity in individuals with impaired FEV(1) (PURE): an international, community-based cohort study. *Lancet Glob Health.*2019;7(5):e613-e623.

7. Fuhlbrigge AL, Kitch BT, Paltiel AD, et al. FEV(1) is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol.* 2001;107(1):61-67.

8. Sharma S, Litonjua AA, Tantisira KG, et al. Clinical predictors and outcomes of consistent bronchodilator response in the childhood asthma management program. *J Allergy Clin Immunol.*2008;122(5):921-928.e924.

9. Tantisira KG, Fuhlbrigge AL, Tonascia J, et al. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. *J Allergy Clin Immunol.* 2006;117(6):1264-1271.

10. Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. *Lancet Respir Med.*2014;2(6):497-506.

11. Wagner PD, Hedenstierna G, Rodriguez-Roisin R. Gas exchange, expiratory flow obstruction and the clinical spectrum of asthma.*Eur Respir J.* 1996;9(6):1278-1282.

12. Racette C, Lu Z, Kowalik K, et al. Lung clearance index is elevated in young children with symptom-controlled asthma. *Health Sci Rep.*2018;1(8):e58.

13. Dominelli PB, Molgat-Seon Y, Foster GE, et al. Quantifying the shape of maximal expiratory flow-volume curves in healthy humans and asthmatic patients. *Respir Physiol Neurobiol.* 2016;220:46-53.

14. Kraan J, van der Mark TW, Koëter GH. Changes in maximum expiratory flow-volume curve configuration after treatment with inhaled corticosteroids. *Thorax.* 1989;44(12):1015-1021.

15. Patel AC, Van Natta ML, Tonascia J, Wise RA, Strunk RC. Effects of time, albuterol, and budesonide on the shape of the flow-volume loop in children with asthma. *J Allergy Clin Immunol.*2008;122(4):781-787.e788.

16. Kapp MC, Schachter EN, Beck GJ, Maunder LR, Witek TJ, Jr. The shape of the maximum expiratory flow volume curve. *Chest.*1988;94(4):799-806.

17. Nève V, Matran R, Baquet G, et al. Quantification of shape of flow-volume loop of healthy preschool children and preschool children with wheezing disorders. *Pediatr Pulmonol.* 2012;47(9):884-894.

18. Zhang Y, Xiong X, Dai F, et al. Curvilinearity of a Maximum Expiratory Flow-Volume Curve: A Useful Indicator for Assessing Airway Obstruction in Children With Asthma. *Respir Care.*2020;65(4):427-436.

19. Park SH, Im MJ, Eom SY, Hahn YS. Accuracy of maximal expiratory flow-volume curve curvilinearity and fractional exhaled nitric oxide for detection of children with atopic asthma. *Korean J Pediatr.*2017;60(9):290-295.

20. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319-338.

21. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J.* 2012;40(6):1324-1343.

22. Ioan I, Coutier L, Bonabel C, et al. Airway obstruction, upper airway artifact and response to bronchodilator in asthmatic and healthy children. *Pediatr Pulmonol.* 2015;50(11):1053-1059.

23. Mead J. Analysis of the configuration of maximum expiratory flow-volume curves. *J Appl Physiol Respir Environ Exerc Physiol.*1978;44(2):156-165.

24. O'Donnell CR, Castile RG, Mead J. Changes in flow-volume curve configuration with bronchoconstriction and bronchodilation. *J Appl Physiol (1985).* 1986;61(6):2243-2251.

25. Weiner DJ, Forno E, Sullivan L, Weiner GA, Kurland G. Subjective and Objective Assessments of Flow-Volume Curve Configuration in Children and Young Adults. *Ann Am Thorac Soc.* 2016;13(7):1089-1095.

26. Strömberg NO, Gustafsson PM. Ventilation inhomogeneity assessed by nitrogen washout and ventilation-perfusion mismatch by capnography in stable and induced airway obstruction. *Pediatr Pulmonol.*2000;29(2):94-102.

27. Ballester E, Reyes A, Roca J, Guitart R, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. *Thorax.* 1989;44(4):258-267.

28. Aurora P, Stocks J, Oliver C, et al. Quality control for spirometry in preschool children with and without lung disease. *Am J Respir Crit Care Med.* 2004;169(10):1152-1159.

29. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med.* 2019;200(8):e70-e88.

Hosted file

`Berrier-et-al-Tables.docx` available at https://authorea.com/users/353761/articles/477514-assessment-of-bronchial-obstruction-and-its-reversibility-by-shape-indexes-of-the-flow-volume-loop-in-asthmatic-children