Correlation of Spirometry and Symptom Scores in Childhood Asthma and the Usefulness of Curvature Assessment in Expiratory Flow-Volume Curves

Johannes H Wildhaber MD PhD,* Josué Sznitman MSc,* Paul Harpes PhD, Daniel Straub MD, Alexander Möller MD, Pavel Basek MD, and Felix H Sennhauser MD

BACKGROUND: Spirometry, and in particular forced expiratory volume in the first second (FEV_1), are standard tools for objective evaluation of asthma. However, FEV_1 does not correlate with symptom scores, and hence its value in the assessment of childhood asthma may be limited. Therefore, some clinicians subjectively assess the presence of curvature in the maximum expiratory flow-volume (MEFV) curves obtained from spirometry, where concave patterns are observable despite normal FEV_1 values. OBJECTIVE: To evaluate the usefulness of subjective and objective measures of the curvature in the descending phase of the MEFV curve for the assessment of asthma. METHODS: We obtained symptom scores and performed spirometry in 48 patients with asthma (21 females, mean ± SD age 10.8 ± 2.4 y). We measured FEV_1, the ratio of FEV_1 to forced vital capacity (FEV_1/FVC), maximum expiratory flow at one quarter of the way, and at halfway, through the forced expiratory maneuver (MEF_{25} and MEF_{50}, respectively), and maximum expiratory flow in the middle half of the forced expiratory maneuver (MEF_{25-75}). Expiratory obstruction was ranked independently by 3 pediatric pulmonologists, by subjective assessment of the MEFV curve. In addition, the curvature of the descending limb of the MEFV curve was quantitatively estimated by introducing an "average curvature index." RESULTS: No significant correlations were found between FEV_1, MEF_{50}, MEF_{25}, and MEF_{25-75}, respectively, and symptom score ($r = -0.22$, $p = 0.14$; $r = -0.23$, $p = 0.11$; $r = -0.28$, $p = 0.057$; $r = -0.27$, $p = 0.06$). A weak correlation was found for FEV_1/FVC and symptom score ($r = -0.33$, $p = 0.021$). However, quantitatively determined average curvature index (ACI) correlated significantly better with measured symptom scores ($r = 0.53$, $p < 0.001$) and were in good agreement with the assessment of expiratory obstruction from subjective curvature assessment. CONCLUSIONS: Our general findings show that individual lung function variables do not correlate well with symptoms, whereas subjective curvature assessment is thought to be helpful. With the average curvature index we have illustrated a potential clinical usefulness of quantifying the curvatures of MEFV curves. *Key words: maximum expiratory flow volume curve, pulmonary function test, spirometry, childhood asthma, average curvature index.* [Respir Care 2007;52(12):1744–1752. © 2007 Daedalus Enterprises]

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Introduction

Asthma guidelines recommend an initial evaluation for the assessment of disease severity, followed by regular re-evaluation for the assessment of disease control.[1,2] Since its original introduction,[3,4] spirometry stands as the most widely performed pulmonary function test and is considered the standard tool for objective assessment of asthma. In particular, forced expiratory volume in the first second (FEV_1) is used not only as an index of airway obstruction[5] in the assessment of disease severity and disease control but also as the primary outcome in clinical studies.[6] However, most children with asthma have FEV_1 values in the normal range (≥ 80% of predicted), independent of disease severity and/or disease control.[6–8] Although lung function is important in identifying those with clinically important disease, FEV_1 and individual symptom score do not correlate well in asthmatic children.[9,10] This result may not be surprising, since FEV_1 is often thought to represent the larger airways and may therefore reflect only limited information on disease activity.[11]

It is hypothesized that lung function variables (FEV_1, the ratio of FEV_1 to forced vital capacity [FEV_1/FVC], maximum expiratory flow at one quarter of the way, and at half way, through the forced expiratory maneuver [MEF_{25} and MEF_{50}, respectively], and maximum expiratory flow in the middle half of the forced expiratory maneuver [MEF_{25-75}]) represent smaller-airways function and correlate better with asthma symptoms.[9,12,13] In current practice, however, given the lack of correlation between lung function variables (mainly FEV_1) and symptoms, it is generally recommended to assess asthma severity and asthma control with multiple lung function variables jointly (FEV_1, FEV_1/FVC, MEF_{50}, MEF_{25}, and MEF_{25-75}).[12–15] However, such variables often lack repeatability and have not proved to be effective markers of flow obstruction.[16]

Given the limitations of single lung function variables and their neglect of global curve information, some clinicians commonly "eyeball" the maximum expiratory flow-volume (MEFV) curve to assess childhood asthma severity, where noticeable curvature may be observed in the MEFV curve, despite a possibly normal FEV_1 value,[17,18] and where it was suggested that obstructive lung disease may be inferred by the degree of curvature of the expiratory limb of the flow-volume curve.[14] However, this approach has been, until now, entirely qualitative and based on a purely visual inspection of spirometric tracings. Alternative methods have been proposed to quantify the degree of curvature in MEFV curves and encompass global curve information, including the "slope-ratio" method, which is based on the instantaneous tangent slope of the flow-volume curve and is sensitive to curvature of the expiratory loop.[19] Other approaches have formulated a usable single index based on the shape of[20] or the area under[21] the MEFV curve. More recently, a "curvature index," k_{max}, based on the mathematical definition of the maximum value of the local curvature, was introduced to quantify the curvilinearity of the flow-volume curve.[22] Although the latter method is promising and constitutes a global curvature measurement based on the results of curve fitting, it is constructed around a somewhat arbitrary definition of the region of curvilinearity. In summary, until now, the mathematical description of the descending phase of the MEFV curve, from which flow limitation may be inferred, has relied largely on empirical approaches (best fitting equations), and the portion of the descending limb to be fitted was rather arbitrarily selected.[4,22]

The aim of the present study was first to evaluate the usefulness of single lung function variables (FEV_1, FEV_1/FVC, MEF_{50}, MEF_{25}, and MEF_{25-75}) with respect to symptom scores, in the assessment of childhood asthma. We then tested and compared the usefulness of the subjective curvature assessment method by 3 pediatric pulmonologists, as well as a more objective curvature assessment method, by introducing a straightforward usable index, the average curvature index (ACI).

Methods

Study Design

A total of 48 patients (21 females, mean ± SD age 10.8 ± 2.4 y) were recruited for the present study. Diagnosis of asthma was based on an initial doctor's diagnosis, a previously measured reversible airway obstruction, and a positive skin-prick test for at least one major inhaled allergen. A previously introduced and validated symptom score, which is in accordance with the clinical criteria defined by the international pediatric asthma consensus group, was administered.[23] This score was chosen because, in contrast to most other validated questionnaires, it does not take any medication or lung function variables into account. The following symptoms are assessed: cough, wheezing, asthma symptoms during sport exercise, absence from school, sleep quality, and frequency of symptoms. The child's asthma is classified as either well-controlled (symptom score zero), mild (symptom score 1–5), moderate (symptom score 6–10), or severe (symptom score 11–16). Spirometry (Masterlab, Jaeger, Würzburg, Germany) was performed according to the American Thoracic Society guidelines.[24] The best curve generated in 3–5 efforts was selected for analysis, based on general profile and assessment of whether the patient made the best possible effort. Lung function variables (FEV_1, FEV_1/FVC, MEF_{50}, MEF_{25}, and MEF_{25-75}) were obtained from the MEFV curves.

In addition, the MEFV curves were independently described by 3 pediatric pulmonologists, by subjective assessment of the curvature of the descending phase of the MEFV curve, beyond the point of peak expiratory flow (PEF).[17,18] The clinicians were blinded to the numbers (lung function variables, et cetera) associated with the expiratory loops, as well as to the status of the subject. Asthma groups discerned via qualitative curvature assessment were classified according to visual inspection of the curvature in the spirometric tracing. Four curvature groups were defined: no curvature, slight curvature, substantial curvature, and extensive curvature. A "no curvature" condition was qualified as such on the observation of a steady linear pattern in the descending phase of the MEFV curve. Curves with a convex pattern in the descending limb were scored as representing mild, moderate, or severe obstruction, depending on the degree of curvature in the profile of the curve.

The present study was approved by our ethics committee, and written consent was obtained from the parents or guardians of all the participants.

Numerical Algorithm

The subjective curvature assessment method ("eyeballing") consists of a clinician's subjective assessment of the degree of curvature in the descending limb of the MEFV curve. A direct mathematical translation of this method may then best correspond to the quantitative evaluation of the average curvature over the descending limb of the MEFV curve. The following steps are undertaken to numerically evaluate the ACI. We first determine the region of the MEFV curve to be quantitatively assessed. Raw data are obtained from the spirometer and are characterized with uniform equidistant discrete points (measures are obtained with a uniform volume incremental step of 0.04 L). Each MEFV curve can then be mathematically described by a discrete function, flow = f(V), consisting of n discrete points, where V is the expired volume.

Noise, presumably unrelated to mechanisms of flow limitation, is inherently present in the raw flow-volume data and limits the degree to which local features present in the MEFV curves may be characterized. Fluctuations may arise from instrument noise, rapid flow oscillations due to audible turbulence, or possibly from lack of best effort from the patient (eg, because of coughing). In the present study, we were interested in obtaining continuous and smooth first and second derivatives (f' and f'', respectively) of the MEFV curves with respect to volume, so we first used a nonparametric smoothing spline algorithm over the flow-volume curve, which yields piecewise polynomials with smooth and continuous derivatives.[25]

Characteristic results for f'' (Fig. 1) indicate that the set of MEFV curves investigated here illustrate a surprisingly similar behavior. Namely, spirometric tracings may be distinguished into 2 distinct regions: (1) the region that begins at the start of the expiratory maneuver corresponds to the monotonically ascending portion of the curve where $f'' < 0$, which implies, by mathematical definition,[26] that the (effort-dependent) ascending phase of the MEFV curve with the "hat-shaped" region that contains PEF is concave (also sometimes referred to as "concave down"), as illustrated in Figure 2, and (2) the region of the second derivative function, where $f'' > 0$, implies that the greater lower portion of the descending (effort-independent) limb of the MEFV curve is, by mathematical definition, convex (sometimes referred to as "concave up"). Concave ($f'' < 0$) and convex ($f'' > 0$) regions of a smooth and continuous curve must furthermore be separated, by mathematical definition, at a uniquely defined inflection point, where the condition $f'' = 0$ must be satisfied. Indeed, between the 2 distinct regions of the f'' curve, there can exist only one inflection point. MEFV curves obtained here may then be adequately described by (1) an initial ascending effort-dependent concave region ($f'' < 0$), (2) an inflection point beyond the moment of PEF ($f'' = 0$), and (3) a convex region over the descending effort-independent phase of the MEFV curve ($f'' > 0$).

In practice, the precise location of the inflection point may be made difficult by second derivative functions that exhibit oscillations or an overshoot about the abscissa. This is observed in the examples of second derivative curves in Figure 1, where curves intersect the abscissa several times ($y = 0$), therefore presumably leading to multiple inflection points. To uncover the baseline characteristic behavior of the second derivative curves, a low-pass digital filter is first implemented over the function

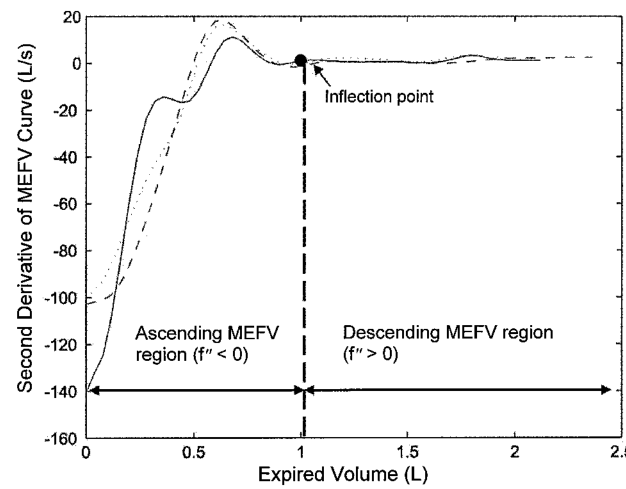

Fig. 1. Second derivative of the maximum expiratory flow-volume (MEFV) curve plotted for clearness of 3 patient curves. The plots yield a characteristic well-defined behavior in which the values of the second derivative of the MEFV curve (f'') settles towards a constant positive value in the vicinity of the abscissa. Note that for the patients illustrated here the inflection points are near to each other.

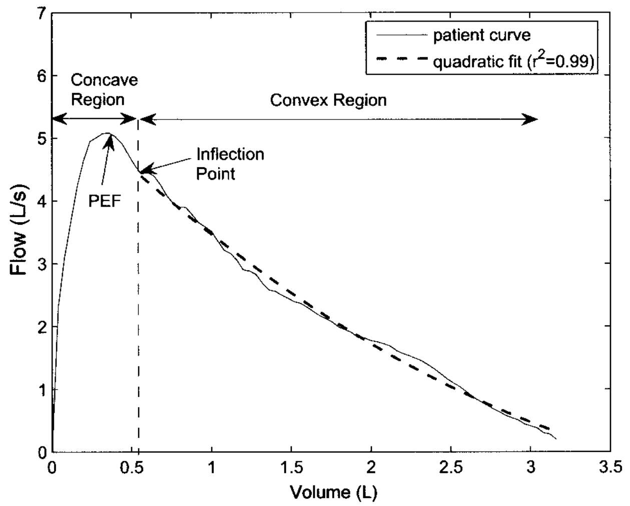

Fig. 2. Example of a maximum expiratory flow-volume (MEFV) curve, with identification of the concave and convex regions and the inflection point. The quadratic fit is shown over the convex region (average curvature index = 0.083). PEF = peak expiratory flow.

f''.[27] The unique solution to $f'' = 0$ may then be easily obtained. For the MEFV curves investigated here, we typically observed beyond the inflection point an approximately constant positive steady-state value of the second derivative (beyond the inflection point, f'' curves are nearly horizontal lines parallel to the abscissa [see Fig. 1]). Based on the observed behavior of f'' over the descending limb of MEFV curves, we may assume that a function $f'' = C$ (where $C > 0$ is a constant) describes with some confidence this portion of the curve. Therefore, integrating f'' twice with respect to volume over the interval ranging from the inflection point to the end point of the flow-volume curve, the descending limb may be described by the quadratic function:

$$\text{flow} = (a \times V^2) + (b \times V) + c$$

where the constants a, b, and c may be solved for each patient. Subsequently, the convex region ($f'' > 0$) of the MEFV curve may be fitted with a polynomial of degree 2 (quadratic function), using a robust least-squares method with a trust-region algorithm.[28] In particular, using a quadratic fitting approach over the region of interest of the MEFV curve beyond the inflection point, regression convergence is highly successful, and variable values are easy to evaluate. Moreover, no data smoothing of the raw MEFV curves, flow = f(V), is needed prior to the fitting scheme (data smoothing is only required to identify the location of the inflection point).

It is precisely the convex region beyond the inflection point that is typically "eyeballed" by some clinicians. Based on our quadratic function fitting scheme, we proceed with the computational steps toward evaluating the ACI. First, the local curvature, κ(V), must be obtained over the fitted convex region. Mathematically, the local curvature at any point of the curve corresponds to the derivative of its tangential angle with respect to the curve's arc length (length along the curve). For a 2-dimensional curve written in the form flow = f(V), the equation of the local curvature becomes $\kappa(V) = f''/(1 + (f')^2)^{3/2}$.[27] Following Bridgeman,[29] the ACI is derived from κ(V) and is mathematically defined as ACI = $\int(\kappa\ ds)/L$, where L is the length of the convex region of the curve, ds describes the arc length of the convex curve, and the integration scheme is carried over the interval ranging from the inflection point to the end point of the MEFV curve. Therefore, ACI encompasses global curve information over the descending phase of the MEFV curve and simultaneously delivers a straightforward, reproducible, and normalized index (ACI is a line integral normalized by the arc length of the region of interest), such that ACI may be compared between patients independent of total expired volume. Figure 2 illustrates an example of a patient MEFV curve and corresponding inflection point, quadratic fit, and resulting ACI value. ACI was computed with Matlab 7.0.4 (The Mathworks, Novi, Michigan).

Interpretation of the Average Curvature Index

Although a complete derivation of a suitable expiratory flow model related to physiology lies beyond the scope of the present study, it may be qualitatively shown, using a simple single-compartment lumped variable model to describe the descending limb of the MEFV curve,[30] that the second derivative (f'') of the MEFV curve is dependent on flow resistance, such that MEFV profiles with a stronger degree of curvature yield higher values of f'' (and consequently larger ACI values). As seen in the previous section, the local curvature, κ(V), is directly proportional to f'', such that higher flow resistance yields effectively higher curvature values. Geometrically, local curvature is given by the reciprocal of the radius of a circle fitted to the curve at a given point. The circle is then fitted such that it shares the same first and second derivative with the curve at that point. This geometrical concept of curvature might describe more appropriately what meets the clinician's eye, compared to the sole use of the mathematical second derivative (f'') of the MEFV curve. ACI then corresponds to the integration of the local curvature, κ(V), along the arc length, ds, of the descending limb, and averaged over the length, L, of the descending limb, and furthermore yields a measure of relative flow limitation while encompassing global curve information over the descending phase of the MEFV curve.

Statistical Analysis

Continuous variables are summarized as mean ± SD if they are approximately normally distributed, or as median (25th and 75th percentile) if not normally distributed. The values of log (symptom score + 5) and log (ACI + 0.01), as well as all lung functions considered, were found to be approximately normally distributed. The Pearson correlation coefficient (r) is computed as measure of monotone association or measure of agreement between approximately normally distributed variables. A weighted κ (with quadratic weights) is used as a measure of agreement between ordinal scores with more than 2 levels. In order to assess agreement between observer scores (4 levels) and symptom scores, the symptom score is reduced to 4 levels (patient classes are defined as well-controlled, mild, moderate, and severe, which corresponds to the symptom score ranges 0, 1–5, 6–10, and 11–16).

To compare agreement between the continuous ACI and symptom scores with agreements between the ordinal observer and categorized symptom scores, a mean observer score is computed, which has 12 levels and may be considered as approximately normally distributed. Agreement is then measured by the Pearson correlation coefficient between (log) ACI, mean observer score, and (log) symptom score. Further, the ACI score is categorized into 4 levels by using receiver operating characteristic curves; weighted κ values are computed for observer scores, the categorized ACI score, and the categorized symptom score. A p value of < 0.05 was taken to indicate a statistically significant difference. Statistical analyses were performed with statistics software (SPSS 11, SPSS, Chicago, Illinois, and R 2.2.1, Alcatel-Lucent, Murray Hill, New Jersey).

Results

Table 1 shows the baseline characteristics of the study group. Based on symptom scores, the level of asthma severity or control was well-controlled in 7 patients, mild in 26 patients, moderate in 8 patients, and severe in 7 patients (Table 2), which represents the distribution of severity seen in our out-patient clinic.

No significant correlation was found between (log) symptom score values and, respectively, FEV_1 ($r = -0.22$, $p = 0.14$, Fig. 3), MEF_{50} ($r = -0.23$, $p = 0.11$), MEF_{25} ($r = -0.28$, $p = 0.057$), and MEF_{25-75} ($r = -0.27$, $p = 0.06$). A weak correlation was found between (log) symptom score and FEV_1/FVC ($r = -0.33$, $p = 0.021$). The diagnoses by the 3 pulmonologists, based on subjective assessment of the curvature of the descending limb of the MEFV curve, led to some discrepancies when compared to the classification based on symptom score ($\kappa = 0.44$, 0.45, and 0.33, each with $p < 0.001$, see Table 2). In particular, observer 1 assessed 6 curves as having no curvature, 19 with slight curvature, 17 with substantial curvature, and 6 with extensive curvature. Observer 2 assessed 10 curves as having no curvature, 21 with slight curvature, 12 with substantial curvature, and 4 with extensive curvature. Observer 3 assessed 4 curves as having no curvature, 16 with slight curvature, 16 with substantial curvature, and 12 cases with extensive curvature (Fig. 4).

Table 1. Baseline Characteristics of the 48 Study Subjects*

Female (%)	44
Age (y)	10.8 ± 2.4
Height (cm)	143.8 ± 14.4
Weight (kg)	39.1 ± 11.9
FEV_1 (% of predicted)†	88.5 ± 17.1
FEV_1/FVC (% of predicted)†	92.2 ± 10.9
MEF_{50} (% of predicted)†	64.8 ± 26.9
MEF_{25} (% of predicted)†	52.2 ± 27.3
MEF_{25-75} (% of predicted)†	61.7 ± 28.5
Symptom score	5 ± 4
Average curvature index (ACI)	0.106 ± 0.086

*Values are mean ± SD unless otherwise indicated.
†Per Reference 35.
FEV_1 = forced expiratory volume in the first second
FVC = forced vital capacity
MEF_{25} = maximum expiratory flow at one quarter of the way through the forced expiratory maneuver
MEF_{75} = maximum expiratory flow at half way through the forced expiratory maneuver
MEF_{25-75} = maximum expiratory flow in the middle half of the forced expiratory maneuver

Based on the small number of patients studied, we made a preliminary attempt to categorize the severity of airway obstruction with respect to ACI values: little or no airway obstruction would correspond to an average curvature approaching zero ($0 < ACI < 0.05$), which suggests that the expiratory loop is approximately straight or only slightly convex; mild severity in airway obstruction may be found in the range $0.05 \leq ACI < 0.085$; moderate severity in airway obstruction may be globally found in the range $0.085 \leq ACI < 0.15$; we expect severe airway obstruction with an $ACI > 0.15$.

Agreement between the categorized ACI score and patient classes ($\kappa = 0.45$, $p < 0.001$) was comparable to the agreement reached by the clinicians. This result suggests that subjective curvature assessment performed by some clinicians does in fact coincide with the more objective computation of the ACI over the convex region of the MEFV curve. The correlation found between (log) symptom score values and (log) ACI ($r = 0.53$, $p < 0.001$, Fig. 5) is slightly better than that obtained between the (log) mean observer and (log) symptom score ($r = 0.49$, $p < 0.001$).

The mean ± SD values of the ACI computed from the MEFV curves are summarized in Table 1. We note that

Table 2. Kappa Statistics for Groups Discerned by Observers and Symptom Scores and Average Curvature Index Groups and Symptom Scores

	Curvature	Symptom Score Group				Total
		Well-controlled	Mild	Moderate	Severe	
Observer 1 (groups)	None	2	4	0	0	6
	Slight	2	14	2	1	19
	Substantial	2	7	6	2	17
	Extensive	1	1	0	4	6
Total		7	26	8	7	48
$\kappa = 0.44$, $p < 0.001$						
Observer 2 (groups)	None	4	6	0	0	10
	Slight	1	15	4	2	22
	Substantial	2	3	4	3	12
	Extensive	0	2	0	2	4
Total		7	26	8	7	48
$\kappa = 0.45$, $p < 0.001$						
Observer 3 (groups)	None	2	2	0	0	4
	Slight	2	12	1	1	16
	Substantial	2	7	4	3	16
	Extensive	1	5	3	3	12
Total		7	26	8	7	48
$\kappa = 0.33$, $p < 0.001$						
Average curvature index (categorized)	None	3	10	0	0	13
	Slight	1	3	2	0	6
	Substantial	2	9	4	1	16
	Extensive	1	4	2	6	13
Total		7	26	8	7	48
$\kappa = 0.45$, $p < 0.001$						

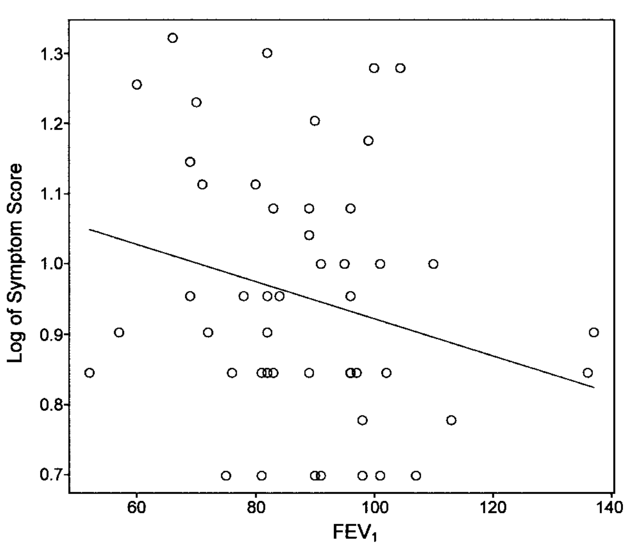

Fig. 3. Log of the symptom score versus forced expiratory volume in the first second (FEV_1). There is no significant correlation between these 2 variables ($r = -0.22$, $p = 0.15$).

ACI values much less than 1 should be expected (ACI = 0.106 ± 0.086) as degrees of curvature in the spirometric tracings remain relatively small, even when they may be qualitatively viewed as "extensive." Indeed, an ACI value = 0 suggests that the descending limb of the curve is perfectly linear (in comparison, a circle of unit radius $r = 1$ has a constant curvature of $1/r = 1$).

Finally, to evaluate the usefulness of the normalization scheme defined in the computation of ACI, we compared correlations obtained between (log) symptom score values and (log) ACI and (log) k_{max}, as well as between (log) ACI and (log) k_{max}, where k_{max} is the curvilinearity index recently proposed by Zheng et al[22] and corresponds to the maximum local curvature. In particular, based on our quadratic fitting scheme, k_{max} is found by first solving the volume, V^*, for which $d\,\kappa(V)/dV = 0$, and substituting such that $k_{max} = \kappa(V^*) = 2a$. Log ($k_{max}$ + 0.1) was found to be approximately normally distributed, and comparing (log) ACI and (log) k_{max} yields a strong correlation ($r = 0.78$, $p < 0.001$). In particular, comparing (log) symptom score values and (log) k_{max} yields a weaker, yet significant, correlation ($r = 0.38$, $p = 0.008$) relative to the one obtained between (log) symptom scores and (log) ACI ($r = 0.53$, $p < 0.001$), which suggests the importance of the normalization scheme implemented for ACI.

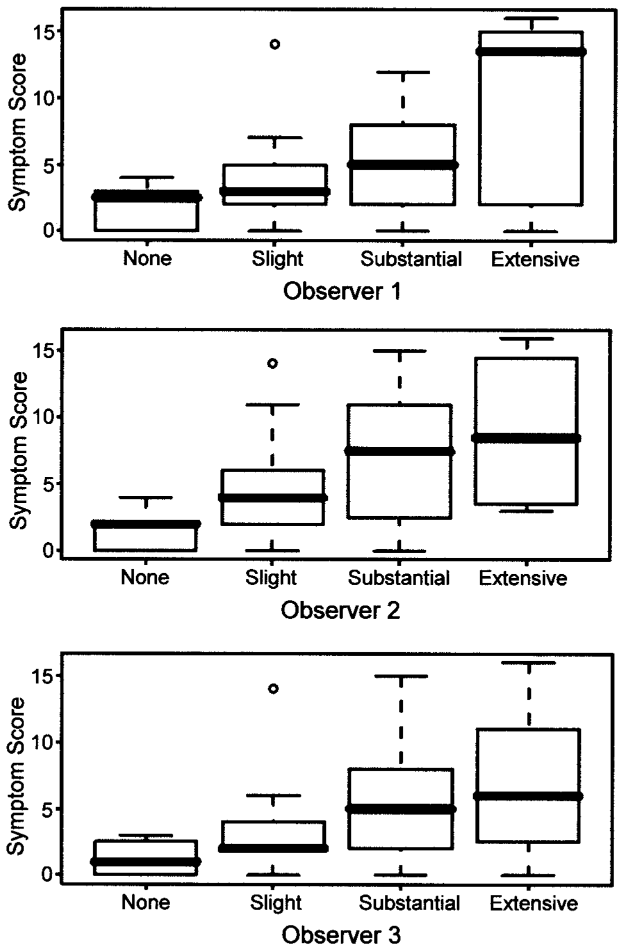

Fig. 4. Box plots of the correlation between symptom scores and asthma severity classes subjectively attributed by 3 observers, based on visual assessment of the curvature in the maximum expiratory flow-volume curve (no curvature, slight curvature, substantial curvature, extensive curvature).

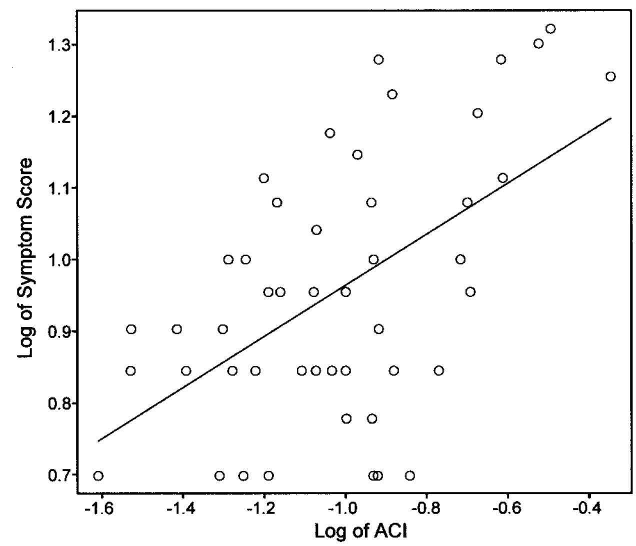

Fig. 5. Log of the symptom score versus log of the average curvature index (ACI). r = 0.53, $p < 0.001$.

Discussion

The present results suggest that measurement of airway obstruction by single lung function variables (mainly FEV_1) does not correlate with asthma symptom scores. There may be various explanations for that finding. Symptom scores are based on patient evaluation and are by definition subjective, such that they cannot serve as an accepted standard. It may well be that some patients do not perceive their symptoms[31] and, hence, as shown in some patients in the present study, though they have substantial MEFV-curve curvature (relatively large ACI value), their symptom scores are low or even zero (see Fig. 5). However, it has also been shown that clinicians can rely on children as young as 7 years old to accurately report changes in symptoms for periods as long as 1 month, and up until age 10, parents will provide important complementary information.[32] The present findings may also be explained in part by the fact that asthma is not solely an obstructive disease, as described by Salter over a century ago,[33] but, rather, asthma is a more complex disease, in which inflammation plays a key role and observing functional changes may not be enough. Perhaps the most important factor is that asthma is a disease of variable airway obstruction.

With our study we have shown that single lung function variables (FEV_1, FEV_1/FVC, MEF_{50}, MEF_{25}, and MEF_{25-75}) do not sufficiently correlate with asthma severity or control assessed via symptom score. There was a slightly better correlation (although significance was not reached) for MEF_{25} and therefore also MEF_{25-75}, which may come from the fact that these variables are thought to represent smaller-airways function.[9,12,13,34] This is also true for FEV_1/FVC, where a weak correlation with symptom scores was found, a ratio introduced by Tiffeneau and Pinelli for the objective measure of airway obstruction.[5] However, we have shown that the subjective assessment of curvature in the descending limb of the MEFV curve by a trained clinician, and in particular the quantitative assessment of the ACI, do correlate significantly better with symptom scores. In particular, ACI may directly serve to support a clinician's subjective assessment of curvature of spirometric tracings with a more objective and reproducible approach. Moreover, we have shown that the normalization scheme of the ACI (with respect to the length of the descending phase of the flow-volume curve) is indeed advantageous and yields better correlation with symptom scores, in comparison with computing the maximum local curvature, k_{max}, following Zheng et al.[22]

Although it is unreasonable to think that any single variable, including ACI, would correlate perfectly with any measured value or reported asthma symptom, the present findings illustrate the hypothesized clinical importance of global curve information (in particular curvature) present in MEFV tracings in the assessment of asthma severity or asthma control. With the introduction of the ACI we have attempted to make use of such curve information, which was thought to be informative[19] but no quantitative method had proven to be clinically useful. With respect to lung function variables, one should note that children with abnormal FEV_1 values are of concern irrespective of whether symptoms are present or not, whereas children with normal FEV_1 values and no symptoms are usually not of any concern. The difficult group remains those with symptoms but normal FEV_1, which may be reflected in the curvature of the spirometric tracing.

We briefly comment on the ACI results we obtained and the limits of the numerical algorithm currently implemented. The numerical computation of ACI is directly dependent on 2 governing factors: the goodness of the quadratic fit of the concave pattern (for all patients studied here, our fits yielded $r^2 > 0.98$), and the correct determination of the location of the inflection point that separates the concave and convex regions of the MEFV curve. The use of the inflection point to delineate the curve to be measured may be potentially flawed because the location of the inflection point may vary with the size of the effort-dependent flow transient that produces the ascending region of the MEFV curve (eg, in patients who have good effort and strength, the achieved PEF can be higher than normal, and a mild concavity in the expiratory part of the flow-volume curve could be over-expressed, resulting in a higher ACI value). Furthermore, as described in our methods section above, smoothing of the raw MEFV data is needed to locate the inflection point, whereas, in contrast, once the inflection point is located, quadratic fitting is performed with the raw MEFV data. This represents a source of potential inconsistency among study groups, which would require more work for standardization in the future.

Nevertheless, to study whether the relative value of the inflection point may be standardized, we here attempted to calculate the inflection point as a function of vital capacity (VC) for our patient data set. We found that the inflection point was at 28.4 ± 10.4% of VC. This result suggests that there may perhaps exist a typical inflection point value that could be defined as the standard point of beginning of the curvature analysis. However, given the relatively wide standard deviation in our result and the small number of patients, we must be cautious in defining a standard inflection point value (percent of VC), and further studies are indeed needed. Moreover, the advantage of the present approach is that, while the computation of the inflection point (and consequently ACI) is specific to each patient curve, ACI may be objectively compared between patients, thanks to our normalization scheme. In particular, the large standard deviation in inflection point values (as a percent of VC) in our data set may actually reflect patient specificities (eg, narrow or wide peaks around PEF in the ascending effort-dependent portion of the MEFV curve alter the relative volume at which the descending, effort-independent, convex region begins).

Both the goodness of the quadratic fit and the determination of the inflection point are themselves contingent upon the profile and the smoothness of the raw data that describes the spirometric tracing. MEFV curves are intrinsically dependent on patients, such that reliable but noisy curves (eg, because the patient coughed or failed to make best effort) cannot be excluded. Therefore, noisy data may significantly deteriorate the objectiveness of the computed ACI and compromise accurate assessment of asthma severity, and large standard deviation values of ACI may limit its utility. Finally, for patient cases where the descending phase of the flow-volume curve is sometimes concave, the inflection point ceases to exist because the entire curve is concave ($f'' < 0$). In such cases the ACI must be revised and defined over a suitable interval (ie, define inflection point as a standardized percent-of-VC value). Generally, improved and more robust algorithms require further development, although we have here shown the usefulness of ACI in the assessment of asthma. Integrating the ACI algorithm within a spirometer could provide immediate ACI values during lung function testing, as opposed to the current post-processing approach.

Conclusions

Based on our recent findings, it seems to be important not to assess asthma severity or asthma control purely based on a single variable of the MEFV curve. Subjective and objective assessments of the overall shape of the MEFV curve provide additional accuracy in the assessment of asthma severity or asthma control, in comparison with the sole use of single lung function variables. Asthma control based mainly on a subjective evaluation by the treating physician was shown to be insufficient or poor in a substantial portion of asthmatic children, despite the availability of highly effective therapies.[35] It is thus not surprising that asthma still imposes a high burden on asthmatic children, caregivers, and society.[36] Therefore, it is of great relevance to find ways to improve asthma control and, hence, to reduce the burden of asthma. In the study by Rabe et al,[35] the evaluation of asthma severity or asthma control was mainly based on reported symptoms, whereas only 40% of the patients had lung function tests performed. The introduction of valid objective measures for the routine management of asthma is likely to be of great value and is likely to improve asthma control. However, it has yet to be proven that these variables provide additional information on disease state or progression, or that objective measures such as the ACI used for disease management are likely to improve the long-term outcomes in asthmatic children.

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