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FEF_{25-75} and FEV_1/FVC in Relation to Clinical and Physiologic Parameters in Asthmatic Children with Normal FEV_1 Values

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Abstract

Background—The assumption that the assessment of FEF_{25-75} does not provide additional information in asthmatic children with normal FEV_1 % predicted has not been adequately tested.

Objective—To determine whether the measurement of the FEF_{25-75} % predicted offers advantages over the FEV_1 % predicted and the FEV_1/FVC % predicted for the evaluation of childhood asthma.

Methods and Measurements—This is a secondary analysis of data from the "Pediatric Asthma Controller Trial" and the "Characterizing the Response to a Leukotriene Receptor Antagonist and Inhaled Corticosteroid" trials. Pearson correlation coefficients, Pearson partial correlation coefficients, canonical correlations, and receiver operator characteristic (ROC) curves were constructed.

Results—Among 437 children with normal FEV_1 % predicted, FEF_{25-75} % predicted and FEV_1/FVC % predicted were (1) positively correlated with $\log_2$ methacholine PC_{20}, (2) positively correlated with morning and evening peak expiratory flow % predicted, and (3) negatively correlated with $\log_{10}$ FeNO and bronchodilator responsiveness. Pearson partial correlations and canonical correlations indicated that FEF_{25-75} % predicted was better correlated with bronchodilator

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responsiveness and $\log_2$ methacholine PC_{20} than were the FEV_1 % predicted or FEV_1/FVC % predicted. In the ROC curve analysis, FEF_{25-75} at 65% predicted had a 90% sensitivity and a 67% specificity for detecting a 20% increase in FEV_1 following albuterol inhalation.

Conclusion—FEF_{25-75} % predicted was well correlated with bronchodilator responsiveness in asthmatic children with normal FEV_1. FEF_{25-75} % predicted should be evaluated in clinical studies of asthma in children, and may be of use in predicting the presence of clinically relevant reversible airflow obstruction.

Keywords

FEF_{25-75}; bronchodilator responsiveness; asthma; FEV_1/FVC; canonical correlations and ROC curves

Introduction

The guidelines of the American Thoracic Society (ATS) do not suggest that the assessment of the forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) plays a significant role in the measurement of airflow obstruction (1,2), and by inference in the clinical assessment of patients with airflow limitation. Recent studies have demonstrated that asthmatic patients may have ventilatory defects in the presence of a normal FEV_1 (3,4). There also are studies that suggest that the FEF_{25-75} is more sensitive as an indicator of symptomatic asthma than the FEV_1 in children (5,6,7) as well as adults (8,9). Since it does not include flows high in the lung volume, the FEF_{25-75} is theoretically less effort-dependent than the FEV_1 and is believed to be a measurement of small airway patency (10,11,12). Similarly, the FEV_1/FVC has been found to correlate with symptoms and medication use in children while the FEV_1 does not (13).

The current study is a secondary analysis of pulmonary function data derived from two multicenter pediatric asthma clinical trials conducted by the Childhood Asthma Research and Education (CARE) Network funded by the NHLBI, entitled “Pediatric Asthma Controller Trial (PACT)” (14) and “Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (CLIC)” trial (15).

The objective of this study is to determine whether the measurement of the FEF_{25-75} in children contributes additional information about clinical variables and airway inflammation to the information obtained from the “gold standard” measurement, the forced expiratory volume in 1 second (FEV_1).

Methods

We evaluated baseline lung function in relation to clinical and physiologic outcome data from two NHLBI Childhood Asthma Research and Education network studies, the Pediatric Asthma Controller (PACT) trial and the Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (CLIC) trial. PACT (14) enrolled 413 children between the ages of 6 to 14 years with mild-to-moderate persistent asthma. There was a 2 to 4 week run-in period. The CLIC trial (15) enrolled 191 children between the ages of 6 to 17 years with mild-to-moderate persistent asthma. There was a 7 to 10 day run-in period. The CLIC trial excluded children with FEV_1 below 70% predicted. Children who completed the run-in periods were potentially eligible for entry into this analysis of baseline and run-in data.

An electronic peak flow meter (AM1; Jaeger-Toennies GmbH, Hoechberg, Germany) was used. Twice-daily entries of asthma symptoms, nighttime awakenings, and rescue albuterol use were recorded in a weekly diary. At the end of the run-in period, the diary and electronic

peak flow meter data were recorded. Subjects with <80% compliance in the diary documentation of peak expiratory flow (PEF) measurements, symptom scores, and albuterol use were excluded. Spirometry was performed by CARE Network-certified pulmonary function technicians with re-reading of results from all sites performed by two individuals following a standardized manual of operation in order to ensure consistency. The tests were performed using a pneumotachograph-type spirometer interfaced with a personal computer system (Jaeger-Toennies GmbH, Hoechberg, Germany). Equipment and testing procedures for the maximal expiratory flow volume maneuvers met American Thoracic Society (ATS) 1994 spirometry standards (15,16) with techniques modified for children less than 8 years of age as described by Eigen et al (17) and Arets et al. (18). Age, gender, and ethnicity appropriate prediction equations (19) were used to calculate percent of predicted values for FEV_1 and forced vital capacity (FVC). Spirometry was performed at least 4 hours after the last use of a short-acting bronchodilator. Bronchodilator responsiveness was tested by repeating spirometry after administering 4 to 8 puffs of albuterol using a valved holding chamber in a graded maximal bronchodilation test. Exhaled nitric oxide was measured using the NIOX® device (Aerocrine Inc, USA, New Providence, NJ) following recommended procedures (21).

Caucasian and African-American children ages 6-7 years were excluded from our analyses because we did not have reliable FEF_{25-75} predicted equations for them. Only baseline and run-in data prior to randomization were analyzed. There were 272 PACT children and 165 CLIC children with sufficient baseline data to be included in these secondary analyses. All of the correlational analyses described below were applied to the combined data set with 272 + 165 = 437 PACT and CLIC children, with an adjustment for the binary indicator of the child's enrolled study.

The baseline measurements were partitioned into two distinct sets. Set 1 consisted of the three spirometric variables (FEV_1 % predicted, FEF_{25-75} % predicted, and FEV_1/FVC % predicted – all pre-bronchodilator). Set 2 consisted of nine variables describing clinical (diary symptoms, diary rescue albuterol use, asthma control questionnaire (ACQ) (22) scores, and prior asthma hospitalization) and physiologic outcomes (morning and evening diary PEF % predicted, maximum bronchodilator (BD) response as % change in FEV_1, methacholine PC_{20}, and exhaled nitric oxide (FeNO). Methacholine PC_{20} values were transformed to $\log_2$ and FeNO values were transformed to $\log_{10}$ in order to normalize their distributions. The % predicted spirometry values that we used in the analyses are adjusted for gender, race, height, and age. All of the correlational analyses described below also are adjusted for asthma duration, age at asthma onset, atopic status, and body mass index

Pearson correlation coefficients and Pearson partial correlation coefficients were constructed between the spirometry variables and the outcome variables. The partial correlation coefficient between a spirometry variable and each of the outcome variables was adjusted for the presence of the remaining two spirometry variables. Thus, the partial correlation coefficient indicates whether a spirometry variable is correlated with an outcome variable after accounting for the other two spirometry variables.

Canonical correlations, a generalization of Pearson correlations, were also performed to determine how two sets of variables relate to one another (23). The Pearson correlation coefficient investigates the linear relationship between one spirometry variable and one outcome variable. The Pearson partial correlation coefficient demonstrates the linear relationship between one spirometric variable and one outcome variable while accounting for the other spirometric variables. There are nine outcome variables and three spirometric variables. Therefore, the Pearson correlations and the Pearson partial correlations do not provide an adequately thorough analysis and interpretation of the complex relationships that may exist between the set of spirometric variables and the set of outcome variables. Canonical

correlation analysis is a multivariate statistical method. It finds the linear combinations of two sets of variables that have the largest Pearson correlation. It is a generalization of a Pearson correlation coefficient and investigates the relationships between the two sets of variables.

The basic steps of a canonical correlation analysis are as follows.

1. The pair of linear combinations of the two sets of variables (Set 1 and Set 2) that has the largest Pearson correlation is determined. This is called Variate Pair 1, and the correlation between the two linear combinations is the first canonical correlation.
2. Variate Pair 2 is the pair of linear combinations that have the largest correlation among all those linear combination pairs that are uncorrelated with Variate Pair 1, yielding the second canonical correlation.
3. This process is continued until the number of Variate Pairs equals the number of variables in the smaller of the two variable sets. With respect to the PACT and CLIC data sets, there were three spirometric variables in Set 1 and nine outcome variables in Set 2. Thus, a maximum of three Variate Pairs and their corresponding canonical correlations can be constructed, although not all three of the canonical correlations actually may be statistically significant. The magnitudes of the coefficients of the variables in the Variate Pairs with significant canonical correlations indicate which variables within Set 1 are strongly correlated with variables within Set 2.

All correlations were performed using the combined data from the PACT and CLIC trials. These analyses were also performed using the data from each trial separately.

Finally, receiver operator characteristic (ROC) curves were calculated for FEF_{25-75} % predicted and FEV_1/FVC % predicted to evaluate their sensitivity and specificity in predicting bronchodilator responsiveness (24). We chose to use a pre- to post-bronchodilator increase in FEV_1 of 20% as the target value for the ROC curve because a 12% response was a potential entry criterion for the CLIC trial and because a 20% increase in FEV_1 represents a clinically relevant response.

The PACT and CLIC data were also analyzed independently so that those analyses could be compared with each other and with the analyses of the combined data.

Results

Table 1 shows the baseline characteristics of CLIC and PACT cohorts. The PACT children were slightly younger, had a shorter duration of asthma, higher FEV_1% predicted, higher FEF_{25-75}% predicted, lower maximum bronchodilator response, lower methacholine response and lower exhaled NO than the CLIC children.

Pearson Correlation Coefficients

The estimated Pearson correlations among the three pre-bronchodilator spirometry variables appear in Table 2. The estimated correlations for the combined PACT and CLIC data were relatively strong, although they did not exceed 0.80. Therefore, multi-collinearity was not an issue of concern in the ensuing analyses and results. Similar results were found when the PACT and CLIC data were analyzed separately (eTables 1 and 2).

The Pearson correlations between the spirometric variables and the outcome variables appear in Table 3. None of the spirometric variables was significantly correlated with asthma symptoms and only FEF_{25-75} and FEV_1/FVC demonstrated small negative correlations with rescue albuterol use. However, all variables did demonstrate significant negative correlations with the ACQ score and FEF_{25-75} demonstrated a small negative correlation with prior asthma

hospitalization. There was a higher level of correlation between the spirometric variables and the physiologic outcomes including morning and evening PEF % predicted, BD response as % change in FEV_1, methacholine PC_{20}, and F_ENO. In general, FEF_{25-75} and FEV_1/FVC % predicted were better correlated with the physiological outcome variables than was FEV_1 % predicted. Indeed, the strongest estimated correlation in Table 3 was between FEF_{25-75} % predicted and maximum BD response, in which r = -0.56 with 95% confidence interval (-0.62, -0.49). Similar results were found when the PACT and CLIC data were analyzed separately (eTables 3 and 4).

Pearson Partial Correlation Coefficients

The Pearson partial correlations also appear in Table 3 (in columns that are adjacent to the Pearson correlations). The Pearson partial correlation between a spirometric variable and an outcome variable is adjusted for the presence of the other two spirometric variables. Table 3 indicates that FEF_{25-75} % predicted and FEV_1/FVC % predicted are not correlated with diary morning and evening PEF % predicted when FEV_1 % predicted is accounted for. In particular, (1) the Pearson correlation between FEF_{25-75} % predicted and diary morning PEF % predicted is 0.28, but the Pearson partial correlation is 0.02, and (2) the Pearson correlation between FEV_1/FVC % predicted and diary morning PEF % predicted is 0.28, but the Pearson partial correlation is 0.06.

The Pearson partial correlation between FEF_{25-75} % predicted and maximum BD response as % change in FEV_1 is not very different from the Pearson correlation −0.49 and -0.56, respectively), whereas the Pearson partial correlation between FEV_1/FVC % predicted and BD response is drastically lower in magnitude than its Pearson correlation (0.12 and −0.38, respectively). This means that there is a strong correlation between the FEF_{25-75} % predicted and the BD response after adjustment for the presence of the other two spirometric variables, FEV_1 % predicted and FEV_1/FVC % predicted. The Pearson partial correlation between FEV_1 % predicted and maximum BD response does not change in magnitude, but it does change in sign (0.23 and −0.24, respectively). Nevertheless, the Pearson partial correlation between FEV_1 % predicted and maximum BD response is much weaker than the Pearson partial correlation between FEF_{25-75} % predicted and maximum BD response (0.23 and −0.49, respectively). Thus, FEF_{25-75} % predicted appears to be the most important of the three spirometric variables in terms of a relationship with maximum BD response as % change in FEV_1.

Canonical Correlation Coefficients

The results of the canonical correlation analysis appear in Table 4. Only the first two canonical correlations are statistically significant (0.65, $p < 0.0001$; 0.46, $p < 0.0001$). For the first canonical correlation, the pair of linear combinations of the spirometric variables (Set 1) and the clinical variables (Set 2) that has the largest Pearson correlation was determined. The standardized coefficients of the canonical correlation indicate that the clinical set of variables depends most on maximum BD response as % change in FEV_1 (-0.61), and, to a lesser extent, on the diary morning PEF % predicted (0.32), and the $\log_2(PC_{20}$ methacholine)(0.41), whereas the spirometric variables depend most on FEF_{25-75} % predicted (0.88). For the second canonical correlation, the pair of linear combinations of the clinical variables and spirometric variables (Variate Pair 2) that has the largest Pearson correlation, while being uncorrelated with Variate Pair 1, was determined. The standardized coefficients of the second canonical correlation indicate that the clinical set of variables depends most on diary morning PEF % predicted (0.82) and the maximum BD response (0.77), whereas the spirometric variables depend most on FEF_{25-75} % predicted (−1.40) and FEV_1 % predicted (1.25). The third canonical correlation is not significant ($p = 0.23$) which indicates that there are no other linear relationships between the clinical and spirometric variables (Variate Pair 3). The canonical correlation analysis

confirms the importance of the relationship between the FEF_{25-75} % predicted and the maximum BD response as % change in FEV_1. Similar results were found when the PACT and CLIC data were analyzed separately (eTables 5 and 6).

Receiver Operator Characteristic (ROC) Curves

Because there is controversy regarding which FEF_{25-75} % predicted value differentiates normal versus abnormal findings, a receiver operator characteristic (ROC) curve of FEF_{25-75} % predicted and BD response as % change in FEV_1 was constructed. The inflection point indicated that the greatest sensitivity and specificity was found with a FEF_{25-75} % predicted of 68%. In particular, the FEF_{25-75} at 68% of predicted had a 94% sensitivity and a 63% specificity for detecting a 20% increase in FEV_1 following albuterol inhalation (Figure 1). The area under the curve = 0.88. For a BD response = 12% increase in FEV_1, the area under the curve = 0.77 with no clear inflection point. Similar results were found when the PACT and CLIC data were analyzed separately (eFigures 1). An ROC curve of FEV_1/FVC % predicted and BD response also was constructed. The inflection point that the greatest sensitivity and specificity for FEV_1/FVC % predicted was found at 95%. The FEV_1/FVC at 95% of predicted had an 87% sensitivity and a 70% specificity for detecting a 20% increase in FEV_1 following albuterol inhalation. The area under the curve = 0.83. A meaningful ROC curve could not be constructed for FEV_1 % predicted which had an area under the curve = 0 0.62 and no inflection point that could be used to indicate the greatest sensitivity and specificity. Similar results were found when the PACT and CLIC data were analyzed separately (eFigure 2).

In order to calculate the number needed to test (NNT), we selected the cut points which yield equivalent values for sensitivity and specificity. The cut point that yields equivalent estimates of sensitivity and specificity for FEF_{25-75} % predicted from its ROC curve is 58.2% (sensitivity = specificity = 0.82). The cut point that yields equivalent estimates of sensitivity and specificity for FEV_1/FVC % predicted is 91.6% (sensitivity = specificity = 0.74). Thus, the NNT = 1/(0.82 − 0.74) = 12.5. In other words, for every 12.5 children in whom measurements of FEF_{25-75} % predicted and FEV_1/FVC % predicted are available, 1 child will be identified who would benefit from bronchodilator based on his/her FEF_{25-75} % predicted measurement that was not identified based on his/her FEV_1/FVC % predicted measurement. An NNT analysis was not performed using the FEV_1 % predicted because its correlation with BD responsiveness was much weaker than that of both the FEF_{25-75} % predicted and the FEV_1/FVC % predicted and ROC curves with FEV_1 % predicted performed too poorly to allow a cut point to be developed for an NNT analysis.

Discussion

Asthma is characterized by inflammation of the large and small airways (25,26). Small airway obstruction has been demonstrated in asthmatic subjects (27,28,29). Exhaled nitric oxide (FeNO) is a measure of airway inflammation in asthma which has been associated with small airway obstruction (30). These two features of asthma are believed to be causally related. Air trapping in asthmatic subjects in the presence of normal FEV_1 has been documented (3,4). The midflow rates measured during spirometric testing are believed to represent small airway airflow (10,28). The measurement of the midflow rate, the FEF_{25-75}, may be a more sensitive indicator of symptomatic childhood asthma than is the FEV_1 (5,6,7). FEF_{25-75} may better reflect small airways disease than the FEV_1 due to peripheral positioning of the airflow choke point in mid-to-low lung volumes and because “slow” lung units contribute gas later in the volume (by definition). The FEF_{25-75} % predicted has been demonstrated to be better correlated with air trapping in asthmatics than the FEV_1 % predicted and the FEV_1/FVC % predicted (4).

We hypothesized that the FEF_{25-75} % predicted would correlate with asthma symptoms, asthma medication use, bronchial hyperreactivity, albuterol-induced bronchodilation and FeNO in two groups of children with mild asthma and normal FEV_1 % predicted. Although the FEF_{25-75} % predicted and FEV_1/FVC % predicted generally performed better than the FEV_1 % predicted, the striking finding was in their ability to predict response to bronchodilator administration. The Pearson partial correlations and the canonical correlation analysis of the combined CLIC and PACT data indicate that the FEF_{25-75} % predicted has stronger relationship with maximum BD response than does the FEV_1/FVC % predicted and the FEV_1 % predicted (partial correlations of −0.49, 0.12, and 0.23, respectively). Further, the estimated correlation of −0.49 is a relatively strong correlation in an analysis of biological variables in a population study.

These findings suggest that high FEF_{25-75} % predicted tends to be associated with normal airway patency with a limited possibility of further bronchodilation. This is in contrast to a high FEV_1 % predicted in our analyses and supports others' findings of airflow obstruction in asthmatic subjects with a normal FEV_1 (3,4).

FEF_{25-75} has previously been found to be significantly low in children with an asthma diagnosis and a history of wheezing (31). These investigators also reported that the FEF_{25-75} was highly correlated with the slope of the methacholine dose-response curve and with degree of methacholine responsiveness, respectively. Our findings are also consistent with those earlier observations. In addition, a previous study by one of our authors found that the FEF_{25-75} was significantly lower in transient early and persistent wheezers when they were reassessed at ages 11 and 16 years (32).

A recent study in a small number of patients with mild asthma demonstrated that FeNO was correlated with closing volume which was used as a measure of small airway obstruction while FeNO was not correlated with % predicted FEV_1 (30). Our results support those findings of a correlation, albeit weak, of small airway patency (FEF_{25-75} in our study) and FeNO in a much larger number of patients with mild asthma. However, unlike that report, but like another earlier study (33), we also found that FeNO also had a weak negative correlation with % predicted FEV_1This latter finding in our subjects is at odds with the previously reported lack of a correlation of FEV_1 % predicted with FeNO (34,35,36). However, the last of these studies in children with persistent asthma, one performed by some of the current investigators, did find a weak negative correlation of FeNO with the FEV_1/FVC ratio. Measures of small airway patency were not reported in those previous studies.

The ROC curve analysis demonstrated that 62 % predicted FEF_{25-75} had a sensitivity of 90% and a specificity of 73% in detecting ≥20% increase in FEV_1 following inhalation of albuterol. The % predicted FEF_{25-75} has a NNT of 7 relative to the FEV_1/FVC % predicted to identify one child who would benefit from bronchodilator testing. This suggests that the FEF_{25-75} is moderately efficacious in identifying otherwise undiagnosed bronchodilator responsiveness. Our finding that the FEF_{25-75} is sensitive and specific for bronchodilator responsiveness is of interest in the context of previous reports that bronchodilator responsiveness predicts an increase in FEV_1 following inhaled corticosteroid treatment (37), and is associated with several indicators of poor asthma control (38,39). This finding may be especially useful to clinicians because this clinically significant increase in FEV_1 suggests suboptimal asthma control, provided that the FVC measurements obtained during multiple spirometric studies are comparable and reproducible. It would be of interest to determine whether the FEF_{25-75} can serve as a surrogate for bronchodilator responsiveness.

What may render the FEF_{25-75} problematic in a given patient is that the variance is much higher than that of the FEV_1. Thus, even though the FEF_{25-75} is more physiologically sensitive, it lacks specificity due to its variability; i.e. the lower limit of normal is substantively lower than

for FEV_1 or FEV_1/FVC. Therefore, it is of limited diagnostic value in detecting an abnormality per se. However, if a patient is already known to have asthma, then the sensitivity of the FEF_{25-75} appears to be valuable in suggesting the likelihood that reversible bronchoconstriction is present. FEV_1/FVC also performed well in predicting bronchodilator response. Ratios of flows divided by volumes, such as the FEV_1/FVC, represent a rate constant and have units of 1/second. The FEV_1/FVC describes the average rate constant over the first second, of the VC. It is likely that one of the reasons that the FEV_1/FVC is so robust is that it averages the rate constants over the first 70%-95% of the FVC in most children with asthma. It has been suggested that the association of the FEV_1/FVC with asthma symptoms and medication use in a previous study was due to the reflection of the increased dysanapsis by the FEV_1/FVC which is present in asthmatics (13). In large studies which have the statistical power to detect low levels of correlation that are statistically significant, or that can compensate for the variability about a mean (SEM) to detect group differences, the FEF_{25-75} is of more use because the variance is compensated for by the large numbers. Under these conditions, the benefit of the increased physiologic sensitivity of the FEF_{25-75} remains.

The strengths of this current study include the large numbers of subjects studied and that all subjects had normal FEV_1 % predicted. A weakness of this study is that we were not able to determine whether FEF_{25-75} predicted the future clinical course since all subjects were treated. Another weakness is that the entry criteria, and therefore the study populations of the CLIC trial and PACT were not identical. The CLIC trial excluded children with FEV_1 <70% predicted and PACT excluded children with FEV_1<80% predicted. A final potential weakness is that unpublished work by Dr. Ron Sorkness (personal communication) suggests a non-linear relationship between FEF_{25-75} and bronchodilator responsiveness. However, this is not a significant factor when the FEV_1 is in the normal range as in our patient groups.

These results suggest that the FEF_{25-75} % predicted should be included among the spirometric data assessed in clinical trials if a 20% bronchodilator response as % change in FEV_1 following albuterol inhalation is not determined. In addition, FEF_{25-75} % predicted is useful to clinicians who have performed spirometry in that it is correlated with bronchodilator responsiveness in children. Its sensitivity is estimated at 90% from the PACT and CLIC studies. These findings need to be verified by additional similar analyses in children. The reproducibility of these results also needs to be tested in data obtained in studies of adult patients.

Conclusion

The FEF_{25-75} % predicted was correlated with bronchodilator responsiveness and methacholine PC_{20} and was sensitive and specific for bronchodilator responsiveness. We believe that the usefulness of the FEF_{25-75} in asthmatic children with normal FEV_1 % predicted should be reevaluated. It appears likely that FEF_{25-75} % predicted can supplement the FEV_1 in the clinical evaluation of mild asthma in such children. In addition, this report demonstrates that the FEF_{25-75} % predicted is negatively correlated with FeNO in children with mild asthma and a normal FEV_1 % predicted. These results suggest that FEF_{25-75} % predicted should be evaluated in clinical studies of asthma in children and may be of use in predicting the presence of clinically relevant reversible airflow obstruction.

Clinical Implications or Key Message

The FEF_{25-75} % predicted correlates with, and is sensitive and specific for, bronchodilator responsiveness in asthmatic children with normal FEV_1 % predicted. This is consistent with airway dysfunction despite the presence of a normal FEV_1.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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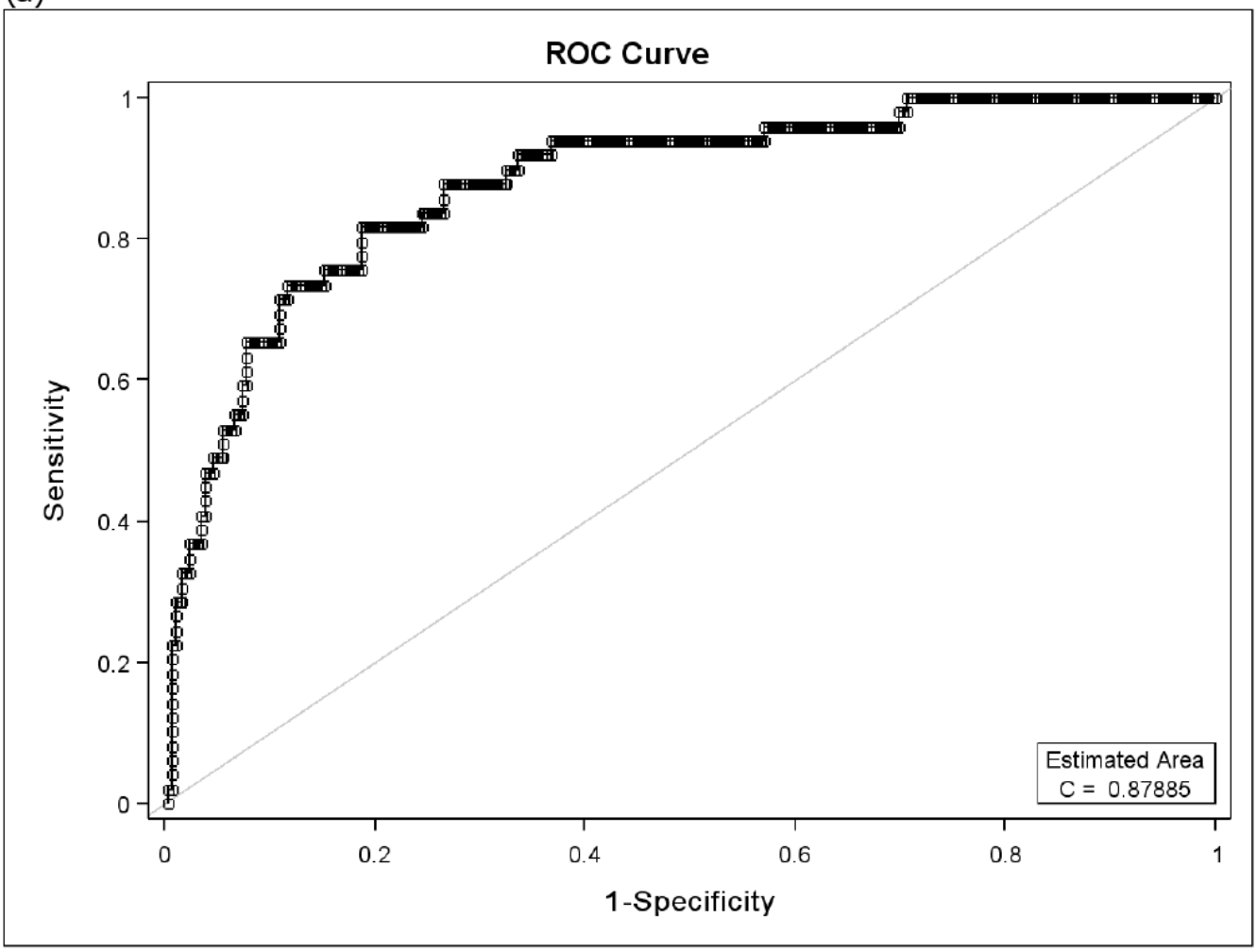
List of Abbreviations/Acronyms

ACQ	Asthma Control Questionnaire
ATS	American Thoracic Society
BD	bronchodilator
CARE Network	Childhood Asthma Research and Education Network
CLIC	Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid
FEF_{25-75}	forced expiratory flow between 25% and 75% of vital capacity
FeNO	exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
NHLBI	National Heart, Lung and Blood Institute
NNT	number needed to treat
PACT	Pediatric Asthma Controller Trial
PC_{20}	provocative concentration that yields a 20% decrease in FEV_1
PEF	peak expiratory flow
ROC	receiver operator characteristic

(a)



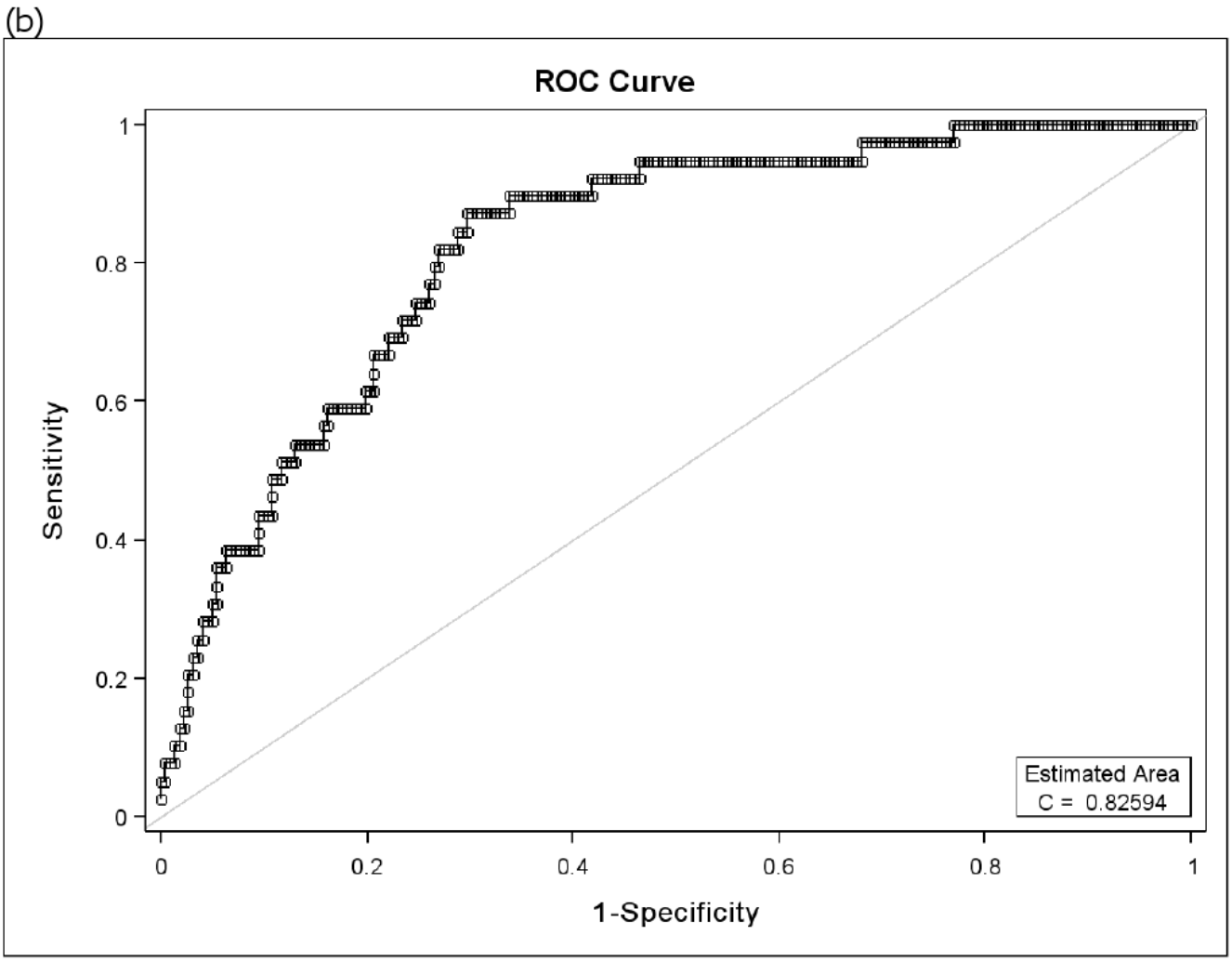


Figure 1.
Receiver Operator Characteristic (ROC) curves of FEF_{25-75} % predicted for bronchodilator responsiveness (BD) as 20% change in FEV_1 (a) and ROC curve of FEV_1/FVC % predicted for BD responsiveness as 20% change in FEV_1 (b). The inflection value for FEF_{25-75} is at 68% predicted and that for the FEV_1/FVC is at 95% predicted. (CLIC and PACT combined)

Table 1

Baseline Characteristics of CLIC and PACT Cohorts

Baseline Characteristic	CLIC	PACT	P-value* comparing CLIC and PACT	CLIC and PACT Combined
Baseline Participants, n	151	328	–-	479
Age, years	12.8 ± 2.8	10.9 ± 1.7	<0.0001	11.5 ± 2.3
Male gender, n (%)	91 (60.3%)	201 (61%)	0.8323	292 (61%)
Caucasian, n (%)	111 (74%)	243 (74%)	0.8940	354 (74%)
Hispanic or Latino, n (%)	40 (27%)	82 (25%)	0.7280	122 (25%)
BMI (kg/m^2)	21.8 ± 5.6	21.1 ± 5.1	0.2008	21.3 ± 5.3
Duration of Asthma, years	7.6 ± 4.0	6.5 ± 3.3	0.0017	6.8 ± 3.6
Spirometry Outcomes				
FEV_1 % Predicted	93.9 ±14.3	98.2 ± 12.6	0.0030	96.7 ± 13.3
FEF_{25-75} % Predicted	67.3 ± 22.7	73.8 ± 21.4	0.0040	71.4 ± 22.1
FEV_1/FVC % Predicted	90.8 ± 9.6	93.0 ± 8.6	0.0511	92.3 ± 9.0
Clinical Outcomes				
Diary symptoms (Cough and Wheeze), 1 week	0.54 ± 0.43	0.49 ± 0.36	0.2474	0.51 ± 0.38
Diary Rescue Albuterol Use	0.82 ± 1.07	0.82 ± 1.00	0.9928	0.82 ± 1.02
ACQ Score	1.05 ± 0.76	1.14 ± 0.57	0.2485	1.11 ± 0.64
Prior Hospitalizations, past year	0.26 ± 0.44	0.24 ± 0.43	0.5724	0.25 ± 0.43
Diary AM PEF % predicted	76.7 ± 13.4	76.9 ± 15.0	0.8703	76.9 ± 14.4
Diary PM PEF % predicted	79.3 ± 13.4	78.7 ± 15.4	0.6855	78.9 ± 14.7
Physiological Outcomes				
Max BD Response (% Change in FEV_1)	14.9 ± 10.3	9.4 ± 7.2	<0.0001	11.1 ± 8.7
Log_2 (PC_{20} methacholine)	3.3 ± 4.5	2.2 ± 2.8	0.0321	2.5 ± 3.4
Log_{10} (FeNO)	1.5 ± 0.4	1.4 ± 0.4	0.0041	1.4 ± 0.4

* P-value calculated using chi-square test (for categorical variables) or student's t-test (for continuous variables).

Table 2

Confidence Intervals and P-values for Testing Null Correlations Among Spirometry Variables Using Combined PACT and CLIC Baseline Data

	FEV_1 % Pred	**FEF_{25-75} % Pred**	**FEV_1/FVC % Pred**
FEV_1 % Pred		0.69 (0.62, 0.75) p < 0.0001	0.58 (0.50, 0.66) p < 0.0001
FEF_{25-75} % Pred	0.69 (0.62, 0.75) p < 0.0001		0.79 (0.74, 0.83) p < 0.0001
FEV_1/FVC % Pred	0.58 (0.50, 0.66) p < 0.0001	0.79 (0.74, 0.83) p < 0.0001	

Table 3

Pearson Correlation and Partial Correlation Coefficients (with 95% Confidence Intervals and P-values for Testing Null Correlations) of Spirometry Variables with Clinical Variables Using Combined PACT and CLIC Baseline Data

	FEV_1 % Predicted Correlations	**FEV_1 % Predicted Partial Correlations**	**FEV_1 % Predicted Partial Correlations (Partialling out Clinical Variables)**	**FEF25-75 % Predicted Correlations**	**FEV25-75 % Predicted Partial Correlations**	**FEV_1 % Predicted Partial Correlations (Partialling out Clinical Variables)**	**FEV/FVC % Predicted Correlations**	**FEV/FVC % Predicted Partial Correlations**	**FEV_1 % Predicted Partial Correlations (Partialling out Clinical Variables)**
Clinical Outcomes									
Diary Symptoms (Cough and Wheeze)	0.07 (-0.03, 0.17) p = 0.16	0.02 (-0.09, 0.14) p = 0.70	0.01 (-0.12, 0.13) p = 0.92	0.01 (-0.08, 0.11) p = 0.78	-0.01 (-0.13, 0.10) p = 0.78	-0.03 (-0.15, 0.09) p = 0.64	-0.02 (-0.13, 0.10) p = 0.78	0.02 (-0.13, 0.10) p = 0.77	0.04 (-0.09, 0.16) p = 0.54
Diary Rescue Albuterol Use	-0.09 (-0.19, 0.01) p = 0.08	-0.05 (-0.17, 0.06) p = 0.44	-0.06 (-0.18, 0.07) p = 0.38	-0.13 (-0.23, -0.03) p = 0.008	-0.07 (-0.18, 0.05) p = 0.23	-0.05 (-0.18, 0.07) p = 0.40	-0.21 (-0.32, -0.10) p = 0.0002	-0.05 (-0.16, 0.07) p = 0.44	-0.05 (-0.17, 0.08) p = 0.44
ACQ Score	-0.23 (-0.32, -0.13) p < 0.0001	-0.19 (-0.21, 0.02) p = 0.12	-0.10 (-0.22, 0.02) p = 0.10	-0.17 (-0.27, -0.07) p = 0.001	0.04 (-0.07, 0.16) p = 0.49	0.00 (-0.12, 0.13) p = 0.98	-0.23 (-0.33, -0.11) p < 0.0001	-0.14 (-0.25, -0.02) p = 0.02	-0.09 (-0.21, 0.03) p = 0.15
Prior Hospitaliztions	-0.11 (-0.21, 0.01) p = 0.03	0.03 (-0.09, 0.14) p = 0.65	0.03 (-0.09, 0.16) p = 0.59	-0.14 (-0.23, -0.04) p = 0.005	-0.11 (-0.22, 0.01) p = 0.07	-0.08 (-0.20, 0.04) p = 0.19	-0.02 (-0.13, 0.10) p = 0.74	0.07 (-0.04, 0.19) p = 0.21	0.06 (-0.07, 0.18) p = 0.35
Physiological Outcomes									
Diary AM PEF % Predicted	0.38 (0.29, 0.46) p < 0.0001	0.30 (0.19, 0.40) p < 0.0001	0.30 (0.19, 0.40) p < 0.0001	0.28 (0.18, 0.37) p < 0.0001	0.02 (-0.13, 0.10) p = 0.77	-0.01 (-0.12, 0.11) p = 0.89	0.28 (0.17, 0.39) p < 0.0001	0.06 (-0.06, 0.17) p = 0.34	0.04 (-0.07, 0.16) p = 0.47
Diary PM PEF % Predicted	0.35 (0.26, 0.44) p < 0.0001	0.28 (0.17, 0.38) p < 0.0001	0.30 (0.18, 0.40) p < 0.0001	0.24 (0.15, 0.33) p < 0.0001	0.01 (-0.12, -0.11) p = 0.89	0.00 (-0.13, 0.12) p = 0.97	0.23 (0.12, 0.33) p < 0.0001	0.02 (-0.10, 0.13) p = 0.79	0.00 (-0.12, 0.12) p = 0.99
Max BD Response (% Change in FEV_1)	-0.24 (-0.33, -0.14) p < 0.0001	0.23 (0.12, 0.33) p < 0.0001	0.25 (0.13, 0.36) p < 0.0001	**-0.56 (-0.62, -0.49)** p < 0.0001	**-0.49 (-0.58, -0.40)** p < 0.0001	**-0.49 (-0.58, -0.39)** p < 0.0001	-0.38 (-0.47, -0.27) p < 0.0001	0.12 (0.00, 0.23) p = 0.05	0.11 (-0.02, 0.23) p = 0.09
$\log_2$ (PC_{20} methacholine)	0.27 (0.17, 0.37) p < 0.0001	0.10 (-0.03, 0.22) p = 0.12	0.10 (-0.03, 0.22) p = 0.12	0.36 (0.26, 0.45) p < 0.0001	0.16 (0.03, 0.28) p = 0.01	0.15 (0.03, 0.27) p = 0.02	0.40 (0.30, 0.51) p < 0.0001	0.10 (-0.03, 0.22) p = 0.16	0.08 (-0.05, 0.20) p = 0.23
$\log_{10}$(FeNO)	-0.13 (-0.23, -0.03) p = 0.01	0.04 (-0.07, 0.16) p = 0.47	0.07 (-0.05, 0.19) p = 0.27	-0.22 (-0.31, -0.13) p < 0.0001	-0.10 (-0.21, -0.02) p = 0.02	-0.09 (-0.21, 0.03) p = 0.15	-0.25 (-0.35, -0.13) p < 0.0001	-0.09 (-0.20, 0.03) p = 0.13	-0.07 (-0.19, 0.06) p = 0.30

Table 4

Canonical Correlation Analysis Between Spirometry Variables and Clinical Variables Using Combined PACT and CLIC Baseline Data

Combined PACT and CLIC Canonical Variate Pairs			
Standardized Coefficients			
	Variate Pair 1	**Variate Pair 2**	**Variate Pair 3**
Diary AM PEF % Predicted	0.32	0.82	-1.43
Diary PM PEF % Predicted	0.05	-0.22	1.94
Max BD Response (% Change in FEV_1)	-0.61	0.77	-0.17
$\log_2(PC_{20})$	0.41	0.20	-0.13
Diary Symptoms (Cough and Wheeze)	0.11	0.32	-0.35
Diary Rescue Albuterol Use	-0.01	-0.14	0.07
$\log_{10}$(Exhaled NO)	-0.01	0.07	0.46
ACQ Score	-0.17	-0.37	0.21
Prior Hospitalizations	0.07	0.08	-0.31
FEV_1 % Predicted	0.10	1.25	0.58
FEF_{25-75} % Predicted	0.88	-1.40	0.83
FEV_1/FVC % Predicted	0.06	0.58	-1.54
Canonical Correlation	0.65 $p < 0.0001$	0.46 $p < 0.0001$	0.20 $p = 0.23$